

### WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



#### INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| (51) International Patent Classification <sup>6</sup> :  |                       | (i1) International Publication Number: WO 97/13  |  |
|--|-----------------------|--|--|
| C12N 15/11, 9/00, 5/10   | A2                    | (43) International Publication Date: 1 May 1997 (01.05.9   |  |
| 21) International Application Number: PCT/US: 22) International Filing Date: 25 October 1996 (2)   |                       | BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, M  |  |
| 30) Priority Data:<br>60/005,974 26 October 1995 (26.10.95)<br>08/584,040 11 January 1996 (11.01.96)   |                       | Published  S  Without international search report and to be republished upon receipt of that report.                             |  |
| 71) Applicants: RIBOZYME PHARMACEUTICALS [US/US]; 2950 Wilderness Place, Boulder, CO 803 CHIRON CORPORATION [US/US]; 4560 Horto Emeryville, CA 94608 (US).   | 101 (US               | ).   |  |
| 72) Inventors: PAVCO, Pamela; 705 Barberry Circle, L<br>CO 80026 (US). McSWIGGEN, James; 4866<br>Drive, Boulder, co 80301 (US). STINCHCOMB, D<br>Old Post Road, Boulder, CO 80301 (US). ESCO<br>Jaime; 1470 Livorna Road, Alamo, CA 94507 (US) | Frankler; 720<br>OBED | in  <br> 3   |  |
| 74) Agents: HELLENKAMP, Amy, S. et al.; Lyon & Lyon Suite 4700, 633 West Fifth Street, Los Angeles, CA 2066 (US).  |                       |  |  |
|  |                       |  |  |
| VASCULAR ENDOTHELIAL GROWTH FAC  |                       |  |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract<br>Nucleic acid molecule which modulates the synthesis   | CTOR 1                | RECEPTOR   |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract<br>Nucleic acid molecule which modulates the synthesis   | CTOR 1                | NT OF DISEASES OR CONDITIONS RELATED TO LEVELS OR RECEPTOR  ession and/or stability of an mRNA encoding one or more receptors or |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract<br>Nucleic acid molecule which modulates the synthesis   | CTOR 1                | RECEPTOR   |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract<br>Nucleic acid molecule which modulates the synthesis   | CTOR 1                | RECEPTOR   |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract  Nucleic acid molecule which modulates the synthesis   | CTOR 1                | RECEPTOR   |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract  Nucleic acid molecule which modulates the synthesis   | CTOR 1                | RECEPTOR   |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract<br>Nucleic acid molecule which modulates the synthesis   | CTOR 1                | ession and/or stability of an mRNA encoding one or more receptors of   |  |
| VASCULAR ENDOTHELIAL GROWTH FAC<br>57) Abstract<br>Nucleic acid molecule which modulates the synthesis   | CTOR 1                | RECEPTOR   |  |
| VASCULAR ENDOTHELIAL GROWTH FAC  57) Abstract  Nucleic acid molecule which modulates the synthesis ascular endothelial growth factor.  | CTOR 1                | ession and/or stability of an mRNA encoding one or more receptors of   |  |

Applicants: Jason Francis Conaty et al U.S. Serial No.: 09/887,880

Filed: June 22, 2001 (Exhibit A)

#### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| AM | Armenia                  | GB | United Kingdom               | MW  | Malawi                   |
|----|--------------------------|----|------------------------------|-----|--------------------------|
| AT | Austria                  | GE | Georgia                      | MX  | Mexico                   |
| ΑŪ | Amtralia                 | GN | Guinea                       | NE  | Niger                    |
| BB | Barbados                 | GR | Greece                       | NL  | Netherlands              |
| BE | Belgium                  | HU | Hungary                      | NO  | Norway                   |
| BF | Burkina Faso             | 1E | Ireland                      | NZ  | New Zealand              |
| BG | Bulgaria                 | IT | Italy                        | PL  | Poland                   |
| Ŋ  | Benin                    | JP | Japan                        | PT  | Portugal                 |
| BR | Brazil                   | KE | Kenys                        | RO  | Romania                  |
| 8Y | Beignus                  | KG | Kyrgystan                    | RU  | Russian Federation       |
| CA | Canada                   | KP | Democratic People's Republic | SD  | Sedan                    |
| CF | Central African Republic |    | of Korea                     | SE  | Sweden                   |
| CG | Congo                    | KR | Republic of Korea            | SG  | Singapore                |
| CH | Switzerland              | KZ | Kazakhatan                   | Si  | Slovenia                 |
| Cl | Côte d'Ivoire            | и  | Liechtenstein                | SK  | Slovakia                 |
| CM | Cameroon                 | LK | Sri Lanka                    | SN  | Senegal                  |
| CN | China                    | LR | Liberia                      | SZ  | Swaziland                |
| CS | Czechoslovakia           | LT | Lithuania                    | TD  | Chad                     |
| CZ | Czech Republic           | LU | Laxembourg                   | TG  | Togo                     |
| DE | Germany                  | LV | Larvia                       | TJ  | Tajikistan               |
| DK | Denmark                  | MC | Monaco                       | IT  | Trinidad and Tobago      |
| EE | Estonia                  | MD | Republic of Moldova          | UA  | Ukraine                  |
| ES | Spain                    | MG | Madagascar                   | UG  | Uganda                   |
| FI | Finland                  | ML | Mali                         | US  | United States of America |
| FR | Prance                   | MN | Mongolia                     | UZ. | Uzbekistan               |
| GA | Gabon                    | MR | Mauritania                   | VN  | Viet Nam                 |

1

#### DESCRIPTION

# Method and Reagent for the Treatment of Diseases or Conditions Related to Levels of Vascular Endothelial Growth Factor Receptor

#### Background Of The Invention

This application is a continuation-in-part of Pavco et al., U.S. Serial No. 60/005,974 all of which is hereby incorporated by reference herein (including drawings).

This invention relates to methods and reagents for the treatment of diseases or conditions relating to the levels of expression of vascular endothelial growth factor (VEGF) receptor(s).

The following is a discussion of relevant art, none of which is admitted to be prior art to the present invention.

VEGF, also referred to as vascular permeability factor (VPF) and vasculotropin, is a potent and highly specific mitogen of vascular endothelial cells (for a review see Ferrara, 1993 Trends Cardiovas. Med. 3, 244; Neufeld et al., 1994 Prog. Growth Factor Res. 5, 89). VEGF induced neovascularization is implicated in various pathological conditions such as tumor angiogenesis, proliferative diabetic retinopathy, hypoxia-induced angiogenesis, rheumatoid arthritis, psoriasis, wound healing and others.

VEGF, an endothelial cell-specific mitogen, is a 34-45 kDa glycoprotein with a wide range of activities that include promotion of angiogenesis, enhancement of vascular-permeability and others. VEGF belongs to the platelet-derived growth factor (PDGF) family of growth factors with approximately 18% homology with the A and B chain of PDGF at the amino acid level. Additionally, VEGF contains the eight conserved cysteine residues common to all growth factors belonging to the PDGF family (Neufeld et al., supra). VEGF protein is believed to exist

2

predominantly as disulfide-linked homodimers; monomers of VEGF have been shown to be inactive (Plouet et al., 1989 EMBO J. 8, 3801).

VEGF exerts its influence on vascular endothelial 5 cells by binding to specific high-affinity cell surface receptors. Covalent cross-linking experiments 125I-labeled VEGF protein have led to the identification of three high molecular weight complexes of 225, 195 and 175 kDa presumed to be VEGF and VEGF receptor complexes (Vaisman et al., 1990 J. Biol. Chem. 265, 19461). on these studies VEGF-specific receptors of 180, 150 and 130 kDa molecular mass were predicted. In endothelial cells, receptors of 150 and the 130 kDa have been identi-The VEGF receptors belong to the superfamily of 15 receptor tyrosine kinases (RTKs) characterized by a conserved cytoplasmic catalytic kinase domain and a hydrophylic kinase sequence. The extracellular domains of the VEGF receptors consist of seven immunoglobulin-like domains that are thought to be involved in VEGF binding 20 functions.

The two most abundant and high-affinity receptors of VEGF are flt-1 (fms-like tyrosine kinase) cloned by Shibuya et al., 1990 Oncogene 5, 519 and KDR (kinase-insert-domain-containing receptor) cloned by Terman et al., 1991 Oncogene 6, 1677. The murine homolog of KDR, cloned by Mathews et al., 1991, Proc. Natl. Acad. Sci., USA, 88, 9026, shares 85% amino acid homology with KDR and is termed as flk-1 (fetal liver kinase-1). Recently it has been shown that the high-affinity binding of VEGF to its receptors is modulated by cell surface-associated heparin and heparin-like molecules (Gitay-Goren et al., 1992 J. Biol. Chem. 267, 6093).

VEGF expression has been associated with several pathological states such as tumor angiogenesis, several forms of blindness, rheumatoid arthritis, psoriasis and others. Following is a brief summary of evidence supporting the involvement of VEGF in various diseases:

- 1) Tumor angiogenesis: Increased levels of VEGF gene expression have been reported in vascularized and edema-associated brain tumors (Berkman et al., 1993 J. Clini. Invest. 91, 153). A more direct demostration of the role of VEGF in tumor angiogenesis was demonstrated by Jim Kim et al., 1993 Nature 362,841 wherein, monoclonal antibodies against VEGF were successfully used to inhibit the growth of rhabdomyosarcoma, glioblastoma multiforme cells in nude mice. Similarly, expression of a dominant negative mutated form of the flt-1 VEGF receptor inhibits vascularization induced by human glioblastoma cells in nude mice (Millauer et al., 1994, Nature 367, 576).
- 2) Ocular diseses: Aiello et al., 1994 New Engl. J. Med. 331, 1480, showed that the ocular fluid, of a majority of patients suffering from diabetic retinopathy and other retinal disorders, contains a high concentration of VEGF. Miller et al., 1994 Am. J. Pathol. 145, 574, reported elevated levels of VEGF mRNA in patients suffering from retinal ischemia. These observations support a direct role for VEGF in ocular diseases.
  - 3) <u>Psoriasis:</u> Detmar et al., 1994 J. Exp. Med. 180, 1141 reported that VEGF and its receptors were over-expressed in psoriatic skin and psoriatic dermal microvessels, suggesting that VEGF plays a significant role in psoriasis.
- 4) Rheumatoid arthritis: Immunohistochemistry and in situ hybridization studies on tissues from the joints of patients suffering from rheumatoid arthritis show an increased level of VEGF and its receptors (Fava et al., 1994 J. Exp. Med. 180, 341). Additionally, Koch et al., 1994 J. Immunol. 152, 4149, found that VEGF-specific antibodies were able to significantly reduce the mitogenic activity of synovial tissues from patients suffering from rheumatoid arthritis. These observations support a direct role for VEGF in rheumatoid arthritis.

In addition to the above data on pathological conditions involving excessive angiogenesis, a number of

4

studies have demonstrated that VEGF is both necessary and sufficient for neovascularization. Takashita et al., 1995 J. Clin. Invest. 93, 662, demonstrated that a single injection of VEGF augmented collateral vessel development in a rabbit model of ischemia. VEGF also can induce neovascularization when injected into the cornea. Expression of the VEGF gene in CHO cells is sufficient to confer tumorigenic potential to the cells. Kim et al., supra and Millauer et al., supra used monoclonal antibodies against VEGF or a dominant negative form of flk-1 receptor to inhibit tumor-induced neovascularization.

During development, VEGF and its receptors are associated with regions of new vascular growth (Millauer et al., 1993 Cell 72, 835; Shalaby et al., 1993 J. Clin.

15 Invest. 91, 2235). Furthermore, transgenic mice lacking either of the VEGF receptors are defective in blood vessel formation, infact these mouse do not survive; flk-1 appears to be required for differentiation of endothelial cells, while flt-1 appears to be required at later stages of vessel formation (Shalaby et al., 1995 Nature 376, 62; Fung et al., 1995 Nature 376, 66). Thus, these receptors must be present to properly signal endothelial cells or their precursors to respond to vascularization-promoting stimuli.

All of the conditions listed above, involve extensive vascularization. This hyper-stimulation of endothelial cells may be alleviated by VEGF antagonists. Thus most of the therapeutic efforts for the above conditions have concentrated on finding inhibitors of the VEGF protein.

25

30 Kim et al., 1993 Nature 362, 841 have been successful in inhibiting VEGF-induced tumor growth and angiogenesis in nude mice by treating the mice with VEGF-specific monoclonal antibody.

Koch et al., 1994 J. Immunol. 152, 4149 showed that the mitogenic activity of microvascular endothelial cells found in rheumatoid arthritis (RA) synovial tissue explants and the chemotactic property of endothelial cells

5

from RA synovial fluid can be neutralized significantly by treatment with VEGF-specific antibodies.

Ullrich et al., International PCT Publication No. WO 94/11499 and Millauer et al., 1994 Nature 367, 576 used a soluble form of flk-1 receptor (dominant-negative mutant) to prevent VEGF-mediated tumor angiogenesis in immunodeficient mice.

Kendall and Thomas, International PCT Publication No. WO 94/21679 describe the use of naturally occuring or 10 recombinantly-engineered soluble forms of VEGF receptors to inhibit VEGF activity.

Robinson, International PCT Publication No. WO 95/04142 describes the use of antisense oligonucleotides targeted against VEGF RNA to inhibit VEGF expression.

Jellinek et al., 1994 Biochemistry 33, 10450 describe the use of VEGF-specific high-affinity RNA aptamers to inhibit the binding of VEGF to its receptors.

Rockwell and Goldstein, International PCT Publication No. WO 95/21868, describe the use of anti-VEGF receptor monoclonal antibodies to neutralize the the effect of VEGF on endothelial cells.

#### Summary Of The Invention

25

30

The invention features novel nucleic acid-based techniques [e.g., enzymatic nucleic acid molecules (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, antisense nucleic acids containing RNA cleaving chemical groups (Cook et al., U.S. Patent 5,359,051)] and methods for their use to down regulate or inhibit the expression of receptors of VEGF (VEGF-R).

In a preferred embodiment, the invention features use of one or more of the nucleic acid-based techniques to inhibit the expression of flt-1 and/or flk-1/KDR receptors.

By "inhibit" it is meant that the activity of VEGF-R or level of mRNAs or equivalent RNAs encoding VEGF-R is reduced below that observed in the absence of the nucleic acid. In one embodiment, inhibition with ribozymes

6

preferably is below that level observed in the presence of an enzymatically inactive RNA molecule that is able to bind to the same site on the mRNA, but is unable to cleave that RNA. In another embodiment, inhibition with antisense oligonucleotides is preferably below that level observed in the presence of for example, an oligonucleotide with scrambled sequence or with mismatches.

By "enzymatic nucleic acid molecule" it is meant an RNA molecule which has complementarity in a substrate 10 binding region to a specified gene target, and also has an enzymatic activity which is active to specifically cleave target RNA. That is, the enzymatic RNA molecule is able to intermolecularly cleave RNA and thereby inactivate a target RNA molecule. This complementary regions allow 15 sufficient hybridization of the enzymatic RNA molecule to the target RNA and thus permit cleavage. One hundred percent complementarity is preferred, but complementarity as low as 50-75% may also be useful in this invention. By "equivalent" RNA to VEGF-R is meant to include those 20 naturally occurring RNA molecules in various animals, including human, mice, rats, rabbits, primates and pigs.

By "antisense nucleic acid" it is meant a nonenzymatic nucleic acid molecule that binds to target RNA by means of RNA-RNA or RNA-DNA or RNA-PNA (protein nucleic acid; Egholm et al., 1993 Nature 365, 566) interactions and alters the activity of the target RNA (for a review see Stein and Cheng, 1993 Science 261, 1004).

By "2-5A antisense chimera" it is meant, an antisense oligonucleotide containing a 5' phosphorylated 2'-5'-30 linked adenylate residues. These chimeras bind to target RNA in a sequence-specific manner and activate a cellular 2-5A-dependent ribonuclease which, in turn, cleaves the target RNA (Torrence et al., 1993 Proc. Natl. Acad. Sci. USA 90, 1300).

35 By "triplex DNA" it is meant an oligonucleotide that can bind to a double-stranded DNA in a sequence-specific manner to form a triple-strand helix. Formation of such

7

triple helix structure has been shown to inhibit transcription of the targeted gene (Duval-Valentin et al., 1992 Proc. Natl. Acad. Sci. USA 89, 504).

By "gene" it is meant a nucleic acid that encodes an RNA.

By "complementarity" it is meant a nucleic acid that can form hydrogen bond(s) with other RNA sequence by either traditional Watson-Crick or other non-traditional types (for example, Hoogsteen type) of base-paired interactions.

10

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds in trans (and thus can cleave other RNA molecules) under physiological condi-Table I summarizes some of the characteristics of these ribozymes. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic 20 portion of the molecule that acts to cleave the target Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary basepairing, and once bound to the correct site, enzymatically to cut the target RNA. Strategic cleavage 25 of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets. 30 single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor of gene expression, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target RNA, but also on the 35 mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme.

8

Ribozymes that cleave the specified sites in VEGF-R mRNAs represent a novel therapeutic approach to treat tumor angiogenesis, ocular diseases, rhuematoid arthritis, psoriasis and others. Applicant indicates that ribozymes are able to inhibit the activity of VEGF-R (specifically flt-1 and flk-1/KDR) and that the catalytic activity of the ribozymes is required for their inhibitory effect. Those of ordinary skill in the art will find that it is clear from the examples described that other ribozymes that cleave VEGF-R mRNAs may be readily designed and are within the invention.

In preferred embodiments of this invention, enzymatic nucleic acid molecule is formed in a hammerhead or hairpin motif, but may also be formed in the motif of 15 a hepatitis delta virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA. Examples of such hammerhead motifs are described by Rossi et al., 1992, AIDS Research and Human Retroviruses 8, 183, of hairpin motifs by Hampel et al., EP0360257, 20 Hampel and Tritz, 1989 Biochemistry 28, 4929, and Hampel et al., 1990 Nucleic Acids Res. 18, 299, and an example of the hepatitis delta virus motif is described by Perrotta and Been, 1992 Biochemistry 31, 16; of the RNaseP motif by Guerrier-Takada et al., 1983 Cell 35, 849, Neurospora VS 25 RNA ribozyme motif is described by Collins (Saville and Collins, 1990 Cell 61, 685-696; Saville and Collins, 1991 Proc. Natl. Acad. Sci. USA 88, 8826-8830; Collins and Olive, 1993 Biochemistry 32, 2795-2799) and of the Group I intron by Cech et al., U.S. Patent 4,987,071. 30 specific motifs are not limiting in the invention and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene 35 RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule.

9

In a preferred embodiment the invention provides a method for producing a class of enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of target mRNAs encoding VEGF-R proteins (specifically flt-1 and flk-1/KDR) such that specific treatment of a disease or condition can be provided with either one or several enzymatic nucleic acids. Such enzymatic nucleic acid molecules can be delivered exogenously to specific tissue or cellular targets as required. Alternatively, the ribozymes can be expressed from DNA and/or RNA vectors that are delivered to specific cells.

Synthesis of nucleic acids greater than 100 nucleo-15 tides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. this invention, small nucleic acid motifs (e.g., antisense oligonucleotides, hammerhead or the hairpin ribozymes) are used for exogenous delivery. The simple structure of these molecules increases the ability of the nucleic acid to invade targeted regions of the mRNA structure. these nucleic acid molecules can also be expressed within cells from eukaryotic promoters (e.g., Izant and Weintraub, 1985 Science 229, 345; McGarry and Lindquist, 1986 Proc. Natl. Acad. Sci. USA 83, Sullenger-Scanlon et al., 1991, Proc. Natl. Acad. Sci. USA, 88, 10591-5; Kashani-Sabet et al., 1992 Antisense Res. Dev., 2, 3-15; Dropulic et al., 1992 J. Virol, 66, 1432-41; Weerasinghe et al., 1991 J. Virol, 65, 5531-4; Ojwang et al., 1992 Proc. Natl. Acad. Sci. 10802-6; Chen et al., 1992 Nucleic Acids Res., 20, 4581-9; Sarver et al., 1990 Science 247, 1222-1225; Thompson et al., 1995 Nucleic Acids Res. 23, 2259). Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a ribozyme (Draper

10

et al., PCT W093/23569, and Sullivan et al., PCT W094/02595, both hereby incorporated in their totality by reference herein; Ohkawa et al., 1992 Nucleic Acids Symp. Ser., 27, 15-6; Taira et al., 1991, Nucleic Acids Res., 19, 5125-30; Ventura et al., 1993 Nucleic Acids Res., 21, 3249-55; Chowrira et al., 1994 J. Biol. Chem. 269, 25856).

Such nucleic acids are useful for the prevention of the diseases and conditions discussed above, and any other diseases or conditions that are related to the levels of 10 VEGF-R (specifically flt-1 and flk-1/KDR) in a cell or tissue.

By "related" is meant that the reduction of VEGF-R (specifically flt-1 and flk-1/KDR) RNA levels and thus reduction in the level of the respective protein will relieve, to some extent, the symptoms of the disease or condition.

Ribozymes are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic 20 acid or nucleic acid complexes can be locally administered to relevant tissues ex vivo, or in vivo through injection, infusion pump or stent, with or without their incorporation in biopolymers. In preferred embodiments, the ribozymes have binding arms which are complementary to the 25 sequences in Tables II to IX. Examples of such ribozymes also are shown in Tables II to IX. Examples of such ribozymes consist essentially of sequences defined in these By "consists essentially of" is meant that the active ribozyme contains an enzymatic center equivalent to 30 those in the examples, and binding arms able to bind mRNA such that cleavage at the target site occurs. sequences may be present which do not interfere with such cleavage.

In another aspect of the invention, ribozymes that cleave target RNA molecules and inhibit VEGF-R (specifically flt-1 and flk-1/KDR) activity are expressed from transcription units inserted into DNA or RNA vectors. The

11

recombinant vectors are preferably DNA plasmids or viral vectors. Ribozyme expressing viral vectors could be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, 5 the recombinant vectors capable of expressing the ribozymes are delivered as described above, and persist in target cells. Alternatively, viral vectors may be used that provide for transient expression of ribozymes. vectors might be repeatedly administered as necessary. 10 Once expressed, the ribozymes cleave the target mRNA. Delivery of ribozyme expressing vectors could be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any 15 other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viralbased technique used to deliver a desired nucleic acid.

Other features and advantages of the invention will 20 be apparent from the following description of the preferred embodiments thereof, and from the claims.

#### Description Of The Preferred Embodiments

First the drawings will be described briefly.

#### Drawings

Figure 1 is a diagrammatic representation of the hammerhead ribozyme domain known in the art. Stem II can be ≥ 2 base-pair long.

Figure 2a is a diagrammatic representation of the hammerhead ribozyme domain known in the art; Figure 2b is a diagrammatic representation of the hammerhead ribozyme as divided by Uhlenbeck (1987, Nature, 327, 596-600) into a substrate and enzyme portion; Figure 2c is a similar diagram showing the hammerhead divided by Haseloff and Gerlach (1988, Nature, 334, 585-591) into two portions; and Figure 2d is a similar diagram showing the hammerhead

divided by Jeffries and Symons (1989, Nucl. Acids. Res., 17, 1371-1371) into two portions.

Figure 3 is a diagramatic representation of the general structure of a hairpin ribozyme. Helix 2 (H2) is 5 provided with a least 4 base pairs (i.e., n is 1, 2, 3 or 4) and helix 5 can be optionally provided of length 2 or more bases (preferably 3 - 20 bases, i.e., m is from 1 -20 or more). Helix 2 and helix 5 may be covalently linked by one or more bases (i.e., r is ≥ 1 base). Helix 1, 4 or 10 5 may also be extended by 2 or more base pairs (e.g., 4 -20 base pairs) to stabilize the ribozyme structure, and preferably is a protein binding site. In each instance, each N and N' independently is any normal or modified base and each dash represents a potential base-pairing inter-15 action. These nucleotides may be modified at the sugar, base or phosphate. Complete base-pairing is not required in the helices, but is preferred. Helix 1 and 4 can be of any size (i.e., o and p is each independently from 0 to any number, e.g., 20) as long as some base-pairing is maintained. Essential bases are shown as specific bases in the structure, but those in the art will recognize that one or more may be modified chemically (abasic, base, sugar and/or phosphate modifications) or replaced with another base without significant effect. Helix 4 can be 25 formed from two separate molecules, i.e., without a connecting loop. The connecting loop when present may be a ribonucleotide with or without modifications to its base, sugar or phosphate. "q" is ≥ 2 bases. The connecting loop can also be replaced with a non-nucleotide linker 30 molecule. H refers to bases A, U, or C. Y refers to pyrimidine bases. " \_\_ " refers to a covalent bond.

Figure 4 is a representation of the general structure of the hepatitis delta virus ribozyme domain known in the art.

Figure 5 is a representation of the general structure of the VS RNA ribozyme domain.

13

Figure 6 is a schematic representation of an RNAseH Specifically, the left side of accessibility assay. Figure 6 is a diagram of complementary DNA oligonucleotides bound to accessible sites on the target RNA. Complementary DNA oligonucleotides are represented by broad lines labeled A, B, and C. Target RNA is represented by the thin, twisted line. The right side of Figure 6 is a schematic of a gel separation of uncut target RNA from a cleaved target RNA. Detection of target 10 RNA is by autoradiography of body-labeled, T7 transcript. The bands common to each lane represent uncleaved target RNA; the bands unique to each lane represent the cleaved products.

Figure 7 shows the effect of hammerhead ribozymes 15 targeted against flt-1 receptor on the binding of VEGF to the surface of human microvascular endothelial cells. Sequences of the ribozymes used are shown in Table II; the length of stem II region is 3 bp. The hammerhead ribozymes were chemically modified such that the ribozyme 20 consists of ribose residues at five positions (see Figure 11); U4 and U7 positions contain 2'-NH2 modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions; four nucleotides at the 5' terminus contains phosphorothioate substitutions. Additionally, the 3' end 25 of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose. The results of two separate experiments are shown as separate bars for each set. Each bar represents the average of triplicate samples. The standard deviation is shown with error bars. For the flt-1 data, 500 nM 30 ribozyme (3:1 charge ratio with LipofectAMINE®) was used. Control 1-10 is the control for ribozymes 307-2797, control 11-20 is the control for ribozymes 3008-5585. The Control 1-10 and Control 11-20 represent the treatment of cells with LipofectAMINE® alone without any ribozymes.

Figure 8 shows the effect of hammerhead ribozymes targeted against KDR receptor on the binding of VEGF to KDR on the surface of human microvascular endothelial

35

PCT/US96/17480 WO 97/15662

14

cells. Sequences of the ribozymes used are shown in Table IV; the length of stem II region is 3 bp. The hammerhead ribozymes were chemically modified such that the ribozyme consists of ribose residues at five positions (see Figure 5 11); U4 and U7 positions contain 2'-NH, modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions; four nucleotides at the 5' terminus contains phosphorothicate substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic 10 deoxyribose. The Control 1-10 and Control 11-20 represent the treatment of cells with LipofectAMINE® alone without any ribozymes. Irrel. RZ, is a control experiment wherein the cells are treated with a non-KDR-targeted ribozyme complexed with Lipofectamine®. 200 nM ribozyme (3:1 15 charge ratio with LipofectAMINE®) was used. In addition to the KDR-targeted ribozymes, the effect on VEGF binding of a ribozyme targeted to an irrelevant mRNA (irrel. RZ) is also shown. Because the affinity of KDR for VEGF is about 10-fold lower than the affinity of flt-1 for VEGF, 20 a higher concentration of VEGF was used in the binding assay.

Figure 9 shows the specificity of hammerhead ribozymes targeted against flt-1 receptor. Inhibition of the binding of VEGF, urokinase plasminogen activator (UPA) and 25 fibroblast growth factor (FGF) to their corresponding receptors as a function of anti-FLT ribozymes is shown. The sequence and description of the ribozymes used are as described under Figure 7 above. The average of triplicate samples is given; percent inhibition as calculated below.

Figure 10 shows the inhibition of the proliferation of Human aortic endothelial cells (HAEC) mediated by phosphorothicate antisense oligodeoxynucleotides targeted against human KDR receptor RNA. Cell proliferation (O.D. 490) as a function of antisense oligodeoxynucleotide 35 concentration is shown. KDR 21AS represents a 21 nt phosphorothioate antisense oligodeoxynucleotide targeted against KDR RNA. KDR 21 Scram represents a 21 nt

30

15

phosphorothicate oligodeoxynucleotide having a scrambled sequence. LF represents the lipid carrier Lipofectin.

Figure 11 shows in vitro cleavage of flt-1 RNA by hammerhead ribozymes. A) diagrammatic representation of 5 hammerhead ribozymes targeted against flt-1 RNA. hammerhead (HH) ribozymes were chemically modified such that the ribozyme consists of ribose residues at five positions; U4 and U7 positions contain 2'-NH2 modificathe remaining nucleotide positions contain 10 2'-O-methyl substitutions; four nucleotides at the 5' contains phosphorothicate substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose (designated as 3'-iH). 1358 HH-A and 4229 HH-A contain 3 base-paired stem II 15 region. 1358 HH-B and 4229 HH-B contain 4 base-paired stem II region. B) and C) shows in vitro cleavage kinetics of HH ribozymes targeted against sites 1358 and 4229 within the flt-1 RNA.

Figure 12 shows inhibition of human microvascular 20 endothelial cell proliferation mediated by anti-flt-1 hammerhead ribozymes. A) Diagrammatic representation of hammerhead (HH) ribozymes targeted against sites 1358 and 4229 within the the flt-1 RNA. B) Graphical representation of the inhibition of cell proliferation mediated by 1358HH and 4229HH ribozymes.

Figure 13 shows inhibition of human microvascular endothelial cell proliferation mediated by anti-KDR hammerhead ribozymes. The figure is a graphical representation of the inhibition of cell proliferation mediated by hammerhead ribozymes targeted against sites 527, 730, 3702 and 3950 within the KDR RNA. Irrelevant HH RZ is a hammerhead ribozyme targeted to an irrelevant target. All of these ribozymes, including the Irrelevant HH RZ, were chemically modified such that the ribozyme consists of ribose residues at five positions; U4 and U7 positions contain 2'-NH<sub>2</sub> modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions; four

16

nucleotides at the 5' termini contain phosphorothicate substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose (3'-iH).

Figure 14 shows in vitro cleavage of KDR RNA by hammerhead ribozymes. The hammerhead (HH) ribozymes were chemically modified such that the ribozyme consists of ribose residues at five positions; U4 and U7 positions contain 2'-NH2 modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose (designated as 3'-iH). 726 HH and 527 HH contain 4 base-paired stem II region. Percent in vitro cleavage kinetics as a function of time of HH ribozymes targeted against sites 527 and 726 within the KDR RNA is shown.

Figure 15 shows in vitro cleavage of KDR RNA by hammerhead ribozymes. The hammerhead (HH) ribozymes were chemically modified such that the ribozyme consists of 20 ribose residues at five positions; U4 and U7 positions contain 2'-NH2 modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose (designated as 3'-iH). 3702 HH and 3950 HH contain 4 base-paired stem II region. Percentin vitro cleavage kinetics as a function of time of HH ribozymes targeted against sites 3702 and 3950 within the KDR RNA is shown.

Figure 16 shows in vitro cleavage of RNA by hammer30 head ribozymes that are targeted to sites that are conserved between flt-1 and KDR RNA. The hammerhead (HH) ribozymes were chemically modified such that the ribozyme consists of ribose residues at five positions; U4 and U7 positions contain 2'-NH2 modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose (designated as 3'-iH).

17

FLT/KDR-I HH ribozyme was synthesized with either a 4 base-paired or a 3 base-paired stem II region. FLT/KDR-I HH can cleave site 3388 within flt-1 RNA and site 3151 within KDR RNA. Percent in vitro cleavage kinetics as a function of time of HH ribozymes targeted against sites 3702 and 3950 within the KDR RNA is shown.

Figure 17 shows inhibition of human microvascular endothelial cell proliferation mediated by anti-KDR and anti-flt-1 hammerhead ribozymes. The figure is a graph-10 ical representation of the inhibition of cell proliferation mediated by hammerhead ribozymes targeted against sites KDR sites-527, 726 or 3950 or flt-1 site 4229. The figure also shows enhanced inhibition of cell proliferation by a combination of flt-1 and KDR hammerhead ribo-4229+527, indicates the treatment of cells with both the flt 4229 and the KDR 527 ribozymes. 4229+726. indicates the treatment of cells with both the flt 4229 and the KDR 726 ribozymes. 4229+3950, indicates the treatment of cells with both the flt 4229 and the KDR 3950 20 ribozymes. VEGF -, indicates the basal level of cell proliferation in the absence of VEGF. A, indicates catalytically active ribozyme; I, indicates catalytically inactive ribozyme. All of these ribozymes were chemically modified such that the ribozyme consists of ribose 25 residues at five positions; U4 and U7 positions contain 2'-NH2 modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions; four nucleotides at the termini contain phosphorothioate substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose (3'-iH).

Figure 18 shows the inhibition of VEGF-induced angiogenesis in rat cornea mediated by anti-flt-1 hammerhead ribozyme. All of these ribozymes were chemically modified such that the ribozyme consists of ribose residues at five positions; U4 position contains 2'-C-allyl modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions; four nucleotides at the 5' termini contain

18

phosphorothioate substitutions. Additionally, the 3' end of the ribozyme contains a 3'-3' linked inverted abasic deoxyribose (3'-iH). A decrease in the Surface Area corresponds to a reduction in angiogenesis. VEGF alone, 5 corresponds to treatment of the cornea with VEGF and no ribozymes. Vehicle alone, corresponds to the treatment of the cornea with the carrier alone and no VEGF. control gives a basal level of Surface Area. Active 4229 HH, corresponds to the treatment of cornea with the flt-1 10 4229 HH ribozyme in the absence of any VEGF. This control also gives a basal level of Surface Area. Active 4229 HH + VEGF, corresponds to the co-treatment of cornea with the flt-1 4229 HH ribozyme and VEGF. Inactive 4229 HH + VEGF, corresponds to the co-treatment of cornea with a cata-15 lytically inactive version of 4229 HH ribozyme and VEGF.

#### Ribozymes

Ribozymes of this invention block to some extent VEGF-R (specifically flt-1 and flk-1/KDR) production and can be used to treat disease or diagnose such disease.

20 Ribozymes will be delivered to cells in culture, to cells or tissues in animal models of angiogenesis and/or RA and to human cells or tissues ex vivo or in vivo. Ribozyme cleavage of VEGF-R RNAs (specifically RNAs that encode flt-1 and flk-1/KDR) in these systems may alleviate disease symptoms.

#### Target sites

Targets for useful ribozymes can be determined as disclosed in Draper et al., International PCT Publication No. WO 95/13380, and hereby incorporated by reference 30 herein in totality. Other examples include the following PCT applications which concern inactivation of expression of disease-related genes: WO 95/23225, WO 95/13380, WO 94/02595, incorporated by reference herein. Rather than repeat the guidance provided in those documents here, 35 below are provided specific examples of such methods, not

19

limiting to those in the art. Ribozymes to such targets are designed as described in those applications and synthesized to be tested in vitro and in vivo, as also described.

The sequence of human and mouse flt-1, KDR and/or flk-1 mRNAs were screened for optimal ribozyme target sites using a computer folding algorithm. Hammerhead or hairpin ribozyme cleavage sites were identified. sites are shown in Tables II to IX (all sequences are 5' 10 to 3' in the tables; X can be any base-paired sequence, the actual sequence is not relevant here). The nucleotide base position is noted in the Tables as that site to be cleaved by the designated type of ribozyme. While mouse and human sequences can be screened and ribozymes thereafter designed, the human targeted sequences are of most utility. However, as discussed in Stinchcomb et al., "Method and Composition for Treatment of Restenosis and Cancer Using Ribozymes," filed May 18, 1994, U.S.S.N. 08/245,466, mouse targeted ribozymes may be useful to test 20 efficacy of action of the ribozyme prior to testing in The nucleotide base position is noted in the Tables as that site to be cleaved by the designated type of ribozyme.

Hammerhead or hairpin ribozymes were designed that could bind and cleave target RNA in a sequence-specific manner. The ribozymes were individually analyzed by computer folding (Jaeger et al., 1989 Proc. Natl. Acad. Sci. USA, 86, 7706) to assess whether the ribozyme sequences fold into the appropriate secondary structure.

Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core were eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity.

Referring to Figure 6, mRNA is screened for access-35 ible cleavage sites by the method described generally in Draper et al., PCT WO93/23569, hereby incorporated by reference herein. Briefly, DNA oligonucleotides

complementary to potential hammerhead or hairpin ribozyme cleavage sites were synthesized. A polymerase chain reaction is used to generate substrates for T7 RNA polymerase transcription from human and mouse flt-1, KDR 5 and/or flk-1 cDNA clones. Labeled RNA transcripts are synthesized in vitro from the templates. The oligonucleotides and the labeled transcripts were annealed, RNAseH was added and the mixtures were incubated for the designated times at 37°C. Reactions are stopped and RNA 10 separated on sequencing polyacrylamide gels. The percentage of the substrate cleaved is determined by autoradiographic quantitation using a PhosphorImaging system. From these data, hammerhead or hairpin ribozyme sites are chosen as the most accessible.

15

Ribozymes of the hammerhead or hairpin motif were designed to anneal to various sites in the mRNA message. The binding arms are complementary to the target site sequences described above. The ribozymes were chemically synthesized. The method of synthesis used follows the 20 procedure for normal RNA synthesis as described in Usman 1987 J. Am. Chem. Soc., 109, 7845; Scaringe et et al., al., 1990 Nucleic Acids Res., 18, 5433; and Wincott et al., 1995 Nucleic Acids Res. 23, 2677-2684 and makes use of common nucleic acid protecting and coupling groups, 25 such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. Small scale synthesis were conducted on a 394 Applied Biosystems, Inc. synthesizer using a modified 2.5  $\mu$ mol scale protocol with a 5 min coupling step for alkylsilyl protected nucleotides and 2.5 30 min coupling step for 2'-O-methylated nucleotides. XI outlines the amounts, and the contact times, of the reagents used in the synthesis cycle. A 6.5-fold excess (163  $\mu$ L of 0.1 M = 16.3  $\mu$ mol) of phosphoramidite and a 24-fold excess of S-ethyl tetrazole (238  $\mu$ L of 0.25 M = 35 59.5 µmol) relative to polymer-bound 5'-hydroxyl was used in each coupling cycle. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by

21

colorimetric quantitation of the trityl fractions, were 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer: detritylation solution was 2% TCA in methylene chloride (ABI); capping 5 was performed with 16% N-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution was 16.9 mM I<sub>2</sub>, 49 mM pyridine, 9% water in THF (Millipore). B & J Synthesis Grade acetonitrile was used directly from the reagent bottle. S-Ethyl tetra10 zole solution (0.25 M in acetonitrile) was made up from the solid obtained from American International Chemical, Inc.

Deprotection of the RNA was performed as follows. The polymer-bound oligoribonucleotide, trityl-off, was transferred from the synthesis column to a 4mL glass screw top vial and suspended in a solution of methylamine (MA) at 65 °C for 10 min. After cooling to -20 °C, the supernatant was removed from the polymer support. The support was washed three times with 1.0 mL of EtOH:MeCN:H<sub>2</sub>O/3:1:1, vortexed and the supernatant was then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, were dried to a white powder.

The base-deprotected oligoribonucleotide was resuspended in anhydrous TEA+HF/NMP solution (250  $\mu$ L of a solution of 1.5mL N-methylpyrrolidinone, 750  $\mu$ L TEA and 1.0 mL TEA+3HF to provide a 1.4M HF concentration) and heated to 65°C for 1.5 h. The resulting, fully deprotected, oligomer was quenched with 50 mM TEAB (9 mL) prior to anion exchange desalting.

For anion exchange desalting of the deprotected oligomer, the TEAB solution was loaded onto a Qiagen 500° anion exchange cartridge (Qiagen Inc.) that was prewashed with 50 mM TEAB (10 mL). After washing the loaded cartridge with 50 mM TEAB (10 mL), the RNA was eluted with 2 M TEAB (10 mL) and dried down to a white powder.

Inactive hammerhead ribozymes were synthesized by substituting a U for  $G_5$  and a U for  $A_{14}$  (numbering from

22

Hertel, K. J., et al., 1992, Nucleic Acids Res., 3252).

The average stepwise coupling yields were >98% (Wincott et al., 1995 Nucleic Acids Res. 23, 2677-2684).

Hairpin ribozymes are synthesized in two parts and annealed to reconstruct the active ribozyme (Chowrira and Burke, 1992 Nucleic Acids Res., 20, 2835-2840). Ribozymes are also synthesized from DNA templates using bacteriophage T7 RNA polymerase (Milligan and Uhlenbeck, 1989, 10 Methods Enzymol. 180, 51).

5

All ribozymes are modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992 TIBS 17, 15 34; Usman et al., 1994 Nucleic Acids Symp. Ser. 31, 163). Ribozymes are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Usman et al., PCT Publication No. WO95/23225, the totality of which is hereby incor-20 porated herein by reference) and are resuspended in water.

The sequences of the ribozymes that are chemically synthesized, useful in this study, are shown in Tables II Those in the art will recognize that these to IX. sequences are representative only of many more such 25 sequences where the enzymatic portion of the ribozyme (all but the binding arms) is altered to affect activity. Stem-loop IV sequence of hairpin ribozymes listed in for example Table III (5'-CACGUUGUG-3') can be altered (substitution, deletion, and/or insertion) to contain any 30 sequence, provided a minimum of two base-paired stem structure can form. The sequences listed in Tables II to IX may be formed of ribonucleotides or other nucleotides or non-nucleotides. Such ribozymes are equivalent to the ribozymes described specifically in the Tables.

23

#### Optimizing Ribozyme Activity

Ribozyme activity can be optimized as described by Stinchcomb et al., supra. The details will not be repeated here, but include altering the length of the 5 ribozyme binding arms (stems I and III, see Figure 2c), or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see Eckstein et al., International Publication No. WO 92/07065; Perrault et al., 1990 Nature 344, 565; Pieken et 10 al., 1991 Science 253, 314; Usman and Cedergren, 1992 Trends in Biochem. Sci. 17, 334; Usman et al., International Publication No. WO 93/15187; Rossi et al., International Publication No. WO 91/03162; Beigelman et al., 1995 J. Biol Chem. in press; as well as Sproat, US 15 Patent No. 5,334,711 which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules). Modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical require-20 ments are desired. (All these publications are hereby incorporated by reference herein).

Sullivan, et al., supra, describes the general methods for delivery of enzymatic molecules. RNA Ribozymes may be administered to cells by a variety of 25 methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes 30 may be directly delivered ex vivo to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination is locally delivered by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Sullivan et al., supra and Draper et al., supra which have been incorporated by reference herein.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozymeencoding sequences into a DNA or RNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA 10 polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers. 15 silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990 Proc. Natl. Acad. Sci. U S A, 87, 6743-7; Gao and Huang 1993 Nucleic Acids Res., 20 21, 2867-72; Lieber et al., 1993 Methods Enzymol., 47-66; Zhou et al., 1990 Mol. Cell. Biol., 10, 4529-37; Thompson et al., 1995 supra). Several investigators have demonstrated that ribozymes expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet et 25 al., 1992 Antisense Res. Dev., 2, 3-15; Ojwang et al., 1992 Proc. Natl. Acad. Sci. U S A, 89, 10802-6; Chen et al., 1992 Nucleic Acids Res., 20, 4581-9; Yu et al., 1993 Proc. Natl. Acad. Sci. U S A, 90, 6340-4; L'Huillier et al., 1992 EMBO J. 11, 4411-8; Lisziewicz et al., 1993 30 Proc. Natl. Acad. Sci. U. S. A., 90, 8000-4; Thompson et al., 1995 Nucleic Acids Res. 23, 2259). The above ribozyme transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, 35 viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors).

In a preferred embodiment of the invention, transcription unit expressing a ribozyme that cleaves RNAs that encode flt-1, KDR and/or flk-1 are inserted into a plasmid DNA vector or an adenovirus or adeno-associated 5 virus DNA viral vector or a retroviral RNA vector. Viral vectors have been used to transfer genes and lead to either transient or long term gene expression (Zabner et al., 1993 Cell 75, 207; Carter, 1992 Curr. Opi. Biotech. The adenovirus, AAV or retroviral vector is 3, 533). 10 delivered as recombinant viral particles. The DNA may be delivered alone or complexed with vehicles (as described for RNA above). The recombinant adenovirus or AAV or retroviral particles are locally administered to the site of treatment, e.q., through incubation or inhalation in 15 vivo or by direct application to cells or tissues ex Retroviral vectors have also been used to express ribozymes in mammalian cells (Ojwang et al., 1992 supra; Thompson et al., 1995 supra).

flt-1, KDR and/or flk-1 are attractive nucleic acid-based therapeutic targets by several criteria. The interaction between VEGF and VEGF-R is well-established. Efficacy can be tested in well-defined and predictive animal models. Finally, the disease conditions are serious and current therapies are inadequate. Whereas protein-based therapies would inhibit VEGF activity nucleic acid-based therapy provides a direct and elegant approach to directly modulate flt-1, KDR and/or flk-1 expression.

Because flt-1 and KDR mRNAs are highly homologous in certain regions, some ribozyme target sites are also homologous (see Table X). In this case, a single ribozyme will target both flt-1 and KDR mRNAs. At partially homologous sites, a single ribozyme can sometimes be designed to accomodate a site on both mRNAs by including G/U basepairing. For example, if there is a G present in a ribozyme target site in KDR mRNA at the same position there is an A in the flt-1 ribozyme target site, the

26

ribozyme can be synthesized with a U at the complementary position and it will bind both to sites. The advantage of one ribozyme that targets both VEGF-R mRNAs is clear, especially in cases where both VEGF receptors may contribute to the progression of angiogenesis in the disease state.

"Angiogenesis" refers to formation of new blood vessels which is an essential process in reproduction, development and wound repair. "Tumor angiogenesis" refers to the induction of the growth of blood vessels from surrounding tissue into a solid tumor. Tumor growth and tumor metastasis are dependent on angiogenesis (for a review see Folkman, 1985 supra; Folkman 1990 J. Natl. Cancer Inst., 82, 4; Folkman and Shing, 1992 J. Biol. Chem. 267, 10931).

Angiogenesis plays an important role in other diseases such as arthritis wherein new blood vessels have been shown to invade the joints and degrade cartilage (Folkman and Shing, supra).

"Retinopathy" refers to inflammation of the retina and/or degenerative condition of the retina which may lead to occlusion of the retina and eventual blindness. In "diabetic retinopathy" angiogenesis causes the capillaries in the retina to invade the vitreous resulting in bleeding and blindness which is also seen in neonatal retinopathy (for a review see Folkman, 1985 supra; Folkman 1990 supra; Folkman and Shing, 1992 supra).

#### Example 1: flt-1, KDR and/or flk-1 ribozymes

By engineering ribozyme motifs applicant has designed several ribozymes directed against flt-1, KDR and/or flk-1 encoded mRNA sequences. These ribozymes were synthesized with modifications that improve their nuclease resistance (Beigelman et al., 1995 J Biol. Chem. 270, 25702) and enhance their activity in cells. The ability of ribozymes to cleave target sequences in vitro was evaluated essentially as described in Thompson et al., PCT Publication

27

No. WO 93/23057; Draper et al., PCT Publication No. WO 95/04818.

### Example 2: Effect of ribozymes on the binding of VEGF to flt-1, KDR and/or flk-1 receptors

Several common human cell lines are available that express endogenous flt-1, KDR and/or flk-1. flt-1, KDR and/or flk-1 can be detected easily with monoclonal antibodies. Use of appropriate fluorescent reagents and fluorescence-activated cell-sorting (FACS) will permit direct quantitation of surface flt-1, KDR and/or flk-1 on a cell-by-cell basis. Active ribozymes are expected to directly reduce flt-1, KDR and/or flk-1 expression and thereby reduce VEGF binding to the cells. In this example, human umbelical cord microvascular endothelial cells were used.

#### Cell Preparation:

Plates are coated with 1.5% gelatin and allowed to stand for one hour. Cells (e.g., microvascular endothelial cells derived from human umbilical cord vein) are plated at 20,000 cells/well (24 well plate) in 200 ml growth media and incubated overnight (- 1 doubling) to yield -40,000 cells (75-80% confluent).

#### Ribozyme treatment:

Media is removed from cells and the cells are washed 25 two times with 300 ml 1X PBS: Ca<sup>2+</sup>: Mg<sup>2+</sup> mixture. A complex of 200-500 nM ribozyme and LipofectAMINE® (3:1 lipid: phosphate ratio) in 200 ml OptiMEM® (5% FBS) was added to the cells. The cells are incubated for 6 hr (equivalent to 2-3 VEGF-R turnovers).

#### 30 125 I VEGF binding assay:

The assay is carried out on ice to inhibit internalization of VEGF during the experiment. The media containing the ribozyme is removed from the cells and the cells

28

are washed twice with with 300 ml 1X PBS: Ca<sup>2+</sup>: Mg<sup>2+</sup> mixture containing 1% BSA. Appropriate <sup>125</sup>I VEGF solution (100,000 cpm/well, +/- 10 X cold 1X PBS, 1% BSA) was applied to the cells. The cells are incubated on ice for 1 h. <sup>125</sup>I VEGF-containing solution is removed and the cells are washed three times with with 300 ml 1X PBS: Ca<sup>2+</sup>: Mg<sup>2+</sup> mixture containing 1% BSA. To each well 300 ml of 100 mM Tris-HCl, pH 8.0, 0.5% Triton X-100 was added and the the mixture was incubated for 2 min. The <sup>125</sup>I VEGF-binding was 0 quantitated using standard scintillation counting techniques. Percent inhibition was calculated as follows:

Percent Inhibition =

cpm <sup>125</sup>I VEGF bound by the ribozyme-treated samples x 100
cpm <sup>125</sup>I VEGF bound by the Control sample

# Example 3: Effect of hammerhead ribozymes targeted against flt-1 receptor on the binding of VEGF

Hammerhead ribozymes targeted to twenty sites within flt-1 RNA were synthesized as described above. Sequence of the ribozymes used are shown in Table II; the length of stem II region is 3 bp. The hammerhead ribozymes were chemically modified such that the ribozyme consists of ribose residues at five positions; U4 and U7 positions contain 2'-NH, modifications, the remaining nucleotide positions contain 2'-O-methyl substitutions; four nucleotides at the 5' terminus contains phosphorothicate substitutions. Additionally, 3' end of the ribozyme contains a 3'-3' linked inverted abasic ribose.

Referring to Figure 7, the effect of hammerhead ribozymes targeted against flt-1 receptor on the binding of VEGF to flt-1 on the surface of human microvascular endothelial cells is shown. The majority of the ribozymes tested were able to inhibit the expression of flt-1 and thereby were able to inhibit the binding of VEGF.

In order to determine the specificity of ribozymes 35 targeted against flt-1 RNA, the effect of five anti-flt-1 ribozymes on the binding of VEGF, UPA (urokinase plasmino-

29

gen activator) and FGF (fibroblast growth factor) to their corresponding receptors were assayed. As shown in Figure 9, there was significant inhibition of VEGF binding to its receptors on cells treated with anti-flt-1 ribozymes.

5 There was no specific inhibition of the binding of UPA and FGF to their corresponding receptors. These data strongly suggest that anti-flt-1 ribozymes specifically cleave flt-1 RNA and not RNAs encoding the receptors for UPA and FGF, resulting in the inhibition of flt-1 receptor expression on the surface of the cells. Thus the ribozymes are responsible for the inhibition of VEGF binding but not the binding of UPA and FGF.

## Example 4: Effect of hammerhead ribozymes targeted against KDR receptor on the binding of VEGF

Hammerhead ribozymes targeted to twenty one sites 15 within KDR RNA were synthesized as described above. Sequence of the ribozymes used are shown in Table IV; the length of stem II region is 3 bp. The hammerhead ribozymes were chemically modified such that the ribozyme 20 consists of ribose residues at five positions; U4 and U7 positions contain 2'-NH, modifications, the remaining nucleotide positions contain 2'-0-methyl substitutions; four nucleotides at the 5' terminus contains phosphorothioate substitutions. Additionally, the 3' end of the 25 ribozyme contains a 3'-3' linked inverted abasic deoxyribose.

Referring to Figure 8, the effect of hammerhead ribozymes targeted against KDR receptor on the binding of VEGF to KDR on the surface of human microvascular endothelial cells is shown. A majority of the ribozymes tested were able to inhibit the expression of KDR and thereby were able to inhibit the binding of VEGF. As a control, the cells were treated with a ribozyme that is not targeted towards KDR RNA (irrel. RZ); there was no specific inhibition of VEGF binding. The results from this control experiment strongly suggest that the inhibi-

tion of VEGF binding observed with anti-KDR ribozymes is a ribozyme-mediated inhibition.

# Example 5: Effect of ribozymes targeted against VEGF receptors on cell proliferation

#### 5 <u>Cell Preparation:</u>

24-well plates are coated with 1.5% gelatin (porcine skin 300 bloom). After 1 hr, excess gelatin is washed off of the plate. Microvascular endothelial cells are plated at 5,000 cells/well (24 well plate) in 200 ml growth 10 media. The cells are allowed to grow for ~ 18 hr (~ 1 doubling) to yield ~10,000 cells (25-30% confluent).

#### Ribozyme treatment:

Media is removed from the cells, and the cells are washed two times with 300 ml 1X PBS:  $Ca^{2*}$ :  $Mg^{2*}$  mixture.

- For anti-flt-1 HH ribozyme experiment (Figure 12) a complex of 500 nM ribozyme; 15 mM LFA (3:1 lipid:phosphate ratio) in 200 ml OptiMEM (5% FCS) media was added to the cells. Incubation of cells is carried out for 6 hr (equivalent to 2-3 VEGF receptor turnovers).
- For anti-KDR HH ribozyme experiment (Figure 13) a complex of 200 nM ribozyme; 5.25 mM LFA (3:1 lipid: phosphate ratio) in 200 ml OptiMEM (5% FCS) media was added to the cells. Incubation of cells is carried out for 3 hr.

#### 25 Proliferation:

After three or six hours, the media is removed from the cells and the cells are washed with 300 ml 1X PBS: Ca<sup>2+</sup>: Mg<sup>2+</sup> mixture. Maintenance media (contains dialyzed 10% FBS) +/- VEGF or basic FGF at 10 ng/ml is added to the cells. The cells are incubated for 48 or 72 h. The cells are trypsinized and counted (Coulter counter). Trypan blue is added on one well of each treatment as control.

As shown in Figure 12B, VEGF and basic FGF can stimulate human microvascular endothelial cell proliferation. However, treatment of cells with 1358 HH or 4229 HH ribozymes, targeted against flt-1 mRNA, results in a significant decrease in the ability of VEGF to stimulate endothelial cell proliferation. These ribozymes do not inhibit the FGF-mediated stimulation of endothelial cell proliferation.

Human microvascular endothalial cells were also treated with hammerhead ribozymes targeted against sites 527, 730, 3702 or 3950 within the KDR mRNA. As shown in Figure 13, all four ribozymes caused significant inhibition of VEGF-mediated induction of cell proliferation. No significant inhibition of cell proliferation was observed when the cells were treated with a hammerhead ribozyme targeted to an irrelevant RNA. Additionally, none of the ribozymes inhibited FGF-mediated stimulation of cell proliferation.

These results strongly suggest that hammerhead ribozymes targeted against either flt-1 or KDR mRNA can specifically inhibit VEGF-mediated induction of endothelial cell proliferation.

# Example 6: Effect of antisense oligonucleotides targeted against VEGF receptors on cell proliferation (colorimetric assay)

Following are some of the reagents used in the proliferation assay:

<u>Cells:</u> Human aortic endothelial cells (HAEC) from Clonetics. Cells at early passage are preferably used.

Uptake Medium: EBM (from Clonetics®);1%
L-Glutamine;20 mM Hepes; No serum; No antibiotics.

Growth Medium: EGM (from Clonetics®); FBS to 20%;1% L-Glutamine; 20 mM Hepes.

<u>Cell Plating</u>: 96-well tissue culture plates are 35 coated with 0.2% gelatin (50 ml/well). The gelatin is incubated in the wells at room temperature for 15-30

32

minutes. The gelatin is removed by aspiration and the wells are washed with PBS:Ca<sup>2\*</sup>: Mg<sup>2\*</sup> mixture. PBS mixture is left in the wells until cells are ready to be added. HAEC cells were detached by trypsin treatment and resuspended at 1.25 x 10<sup>4</sup>/ml in growth medium. PBS is removed from plates and 200 ml of cells (i.e. 2.5 x 10<sup>3</sup> cells/well) are added to each well. The cells are allowed to grow for 48 hours before the proliferation assay.

Assay: Growth medium is removed from the wells. The 10 cells are washed twice with PBS:Ca2\*: Mg2\* mixture without A formulation of lipid/antisense oligoantibiotics. nucleotide (antisense oligonucleotide is used here as a non-limiting example) complex is added to each well (100 ml/well) in uptake medium. The cells are incubated for 15 2-3 hours at 37°C in CO<sub>2</sub> incubator. After uptake, 100 ml/well of growth medium is added (gives final FBS concentration of 10%). After approximately 72 hours, 40 ml MTS® stock solution (made as described by manufacturer) was added to each well and incubated at 37°C for 1-3 20 hours, depending on the color development. (For this assay, 2 hours was sufficient). The intensity of color formation was determined on a plate reader at 490 nM.

Phosphorothioate-substituted antisense oligodeoxynucleotides were custom synthesized by The Midland 25 Certified Reagent Company®, Midland, Texas. Following non-limiting antisense oligodeoxynucleotides targeted against KDR RNA were used in the proliferation assay:

KDR 21 AS: 5'-GCA GCA CCT TGC TCT CCA TCC-3'

As shown in Figure 10, proliferation of HAEC cells are specifically inhibited by increasing concentrations of the phosphorothicate anti-KDR-antisense oligodeoxynucleotide. The scrambled antisense oligonucleotide is not expected to bind the KDR RNA and therefore is not expected to inhibit KDR expression. As expected, there is no detectable inhibition of proliferation of HAEC cells

25

treated with a phosphorothicate antisense oligonucleotide with scrambled sequence.

### Example 7: In vitro cleavage of flt-1 RNA by hammerhead ribozymes

Referring to Figure 11A, hammerhead ribozymes (HH) targeted against sites 1358 and 4229 within the flt-1 RNA were synthesized as described above.

#### RNA cleavage assay in vitro:

Substrate RNA was 5' end-labeled using [q-32P] ATP and 10 T4 polynucleotide kinase (US Biochemicals). Cleavage reactions were carried out under ribozyme "excess" conditions. Trace amount (s 1 nM) of 5' end-labeled substrate and 40 nM unlabeled ribozyme were denatured and renatured separately by heating to 90°C for 2 min and snap-cooling 15 on ice for 10-15 min. The ribozyme and substrate were incubated, separately, at 37°C for 10 min in a buffer containing 50 mM Tris-HCl and 10 mM MgCl,. The reaction was initiated by mixing the ribozyme and substrate solutions and incubating at 37°C. Aliquots of 5 ml are taken 20 at regular intervals of time and the reaction is quenched by mixing with equal volume of 2X formamide stop mix. samples are resolved on 20 % denaturing polyacrylamide The results were quantified and percentage of target RNA cleaved is plotted as a function of time.

Referring to Figure 11B and 11C, hammerhead ribozymes targeted against sites 1358 and 4229 within the flt-1 RNA are capable of cleaving target RNA efficiently in vitro.

### Example 8: In vitro cleavage of KDR RNA by hammerhead ribozymes

In this non-limiting example, hammerhead ribozymes targeted against sites 726, 527, 3702 and 3950 within KDR RNA were synthesized as described above. RNA cleavage reactions were carried out in vitro essentially as described under Example 7.

Referring to Figures 14 and 15, all four ribozymes were able to cleave their cognate target RNA efficiently in a sequence-specific manner.

# Example 9: In vitro cleavage of RNA by hammerhead ribo zymes targeted against cleavage sites that are homologous between KDR and flt-1 mRNA

Because flt-1 and KDR mRNAs are highly homologous in certain regions, some ribozyme target sites are also homologous (see Table X). In this case, a single ribozyme will target both flt-1 and KDR mRNAs. Hammerhead ribozyme (FLT/KDR-I) targeted against one of the homologous sites between flt-1 and KDR (flt-1 site 3388 and KDR site 3151) was synthesized as described above. Ribozymes with either a 3 bp stem II or a 4 bp stem II were synthesized.

15 RNA cleavage reactions were carried out in vitro essentially as described under Example 7.

Referring to Figure 16, FLT/KDR-I ribozyme with either a 3 or a 4 bp stem II was able to cleave its target RNA efficiently in vitro.

## 20 Example 10: Effect of multiple ribozymes targeted against both flt-1 and KDR RNA on cell proliferation

Since both flt-1 and KDR receptors of VEGF are involved in angiogenesis, the inhibition of the expression of both of these genes may be an effective approach to inhibit angiogenesis.

Human microvascular endothalial cells were treated with hammerhead ribozymes targeted against sites flt-1 4229 alone, KDR 527 alone, KDR 726 alone, KDR 3950 alone, flt-1 4229 + KDR 527, flt-1 4229 + KDR 726 or flt-1 4229 + KDR 3950. As shown in Figure 17, all the combinations of active ribozymes (A) caused significant inhibition of VEGF-mediated induction of cell proliferation. No significant inhibition of cell proliferation was observed when the cells were treated with a catalytically inactive 35 (I) hammerhead ribozymes. Additionally, cells treated

35

with ribozymes targeted against both flt-1 and KDR RNAsflt-1 4229 + KDR 527; flt-1 4229 + KDR 726; flt-1 4229 +
KDR 3950, were able to cause a greater inhibition of
VEGF-mediated induction of cell proliferation when
compared with individual ribozymes targeted against either
flt-1 or KDR RNA (see flt-1 4229 alone; KDR 527 alone; KDR
726 alone; KDR 3950 alone). This strongly suggests that
treatment of cells with multiple ribozymes may be a more
effective means of inhibition of gene expression.

#### 10 Animal Models

models in which the There are several animal anti-angiogenesis effect of nucleic acids of the present invention, such as ribozymes, directed against VEGF-R mRNAs can be tested. Typically a corneal model has been 15 used to study angiogenesis in rat and rabbit since recruitment of vessels can easily be followed in this normally avascular tissue (Pandey et al., 1995 Science 268: 567-569). In these models, a small Teflon or Hydron disk pretreated with an angiogenesis factor (e.g. bFGF or 20 VEGF) is inserted into a pocket surgically created in the Angiogenesis is monitored 3 to 5 days later. Ribozymes directed against VEGF-R mRNAs would be delivered in the disk as well, or dropwise to the eye over the time course of the experiment. In another eye model, hypoxia 25 has been shown to cause both increased expression of VEGF and neovascularization in the retina (Pierce et al., 1995 Proc. Natl. Acad. Sci. USA. 92: 905-909; Shweiki et al., 1992 J. Clin. Invest. 91: 2235-2243).

In human glioblastomas, it has been shown that VEGF is at least partially responsible for tumor angiogenesis (Plate et al., 1992 Nature 359, 845). Animal models have been developed in which glioblastoma cells are implanted subcutaneously into nude mice and the progress of tumor growth and angiogenesism is studied (Kim et al., 1993 supra; Millauer et al., 1994 supra).

36

Another animal model that addresses neovascularization involves Matrigel, an extract of basement membrane that becomes a solid gel when injected subcutaneously (Passaniti et al., 1992 Lab. Invest. 67: 519-528). When the Matrigel is supplemented with angiogenesis factors such as VEGF, vessels grow into the Matrigel over a period of 3 to 5 days and angiogenesis can be assessed. Again, ribozymes directed against VEGF-R mRNAs would be delivered in the Matrigel.

10 Several animal models exist for screening of antiangiogenic agents. These include corneal vessel formation following corneal injury (Burger et al., 1985 Cornea 4: 35-41; Lepri, et al., 1994 J. Ocular Pharmacol. 10: 273-280; Ormerod et al., 1990 Am. J. Pathol. 137: 1243-1252) 15 or intracorneal growth factor implant (Grant et al., 1993 Diabetologia 36: 282-291; Pandey et al. 1995 supra; Zieche et al., 1992 Lab. Invest. 67: 711-715), vessel growth into Matrigel matrix containing growth factors (Passaniti et al., 1992 supra), female reproductive organ neovascularization following hormonal manipulation (Shweiki et al., 1993 Clin. Invest. 91: 2235-2243), several models involving inhibition of tumor growth in highly vascularized solid tumors (O'Reilly et al., 1994 Cell 79: 315-328; Senger et al., 1993 Cancer and Metas. Rev. 12: 303-324; 25 Takahasi et al., 1994 Cancer Res. 54: 4233-4237; Kim et 1993 supra), and transient hypoxia-induced neovascularization in the mouse retina (Pierce et al., 1995 Proc. Natl. Acad. Sci. USA. 92: 905-909).

The cornea model, described in Pandey et al. supra,

is the most common and well characterized anti-angiogenic agent efficacy screening model. This model involves an avascular tissue into which vessels are recruited by a stimulating agent (growth factor, thermal or alkalai burn, endotoxin). The corneal model would utilize the intrastromal corneal implantation of a Teflon pellet soaked in a VEGF-Hydron solution to recruit blood vessels toward the pellet which can be quantitated using standard microscopic

37

and image analysis techniques. To evaluate their antiangiogenic efficacy, ribozymes are applied topically to
the eye or bound within Hydron on the Teflon pellet
itself. This avascular cornea as well as the Matrigel

(see below) provide for low background assays. While the
corneal model has been performed extensively in the
rabbit, studies in the rat have also been conducted.

The mouse model (Passaniti et al., supra) is a non-tissue model which utilizes Matrigel, an extract of 10 basement membrane (Kleinman et al., 1986) or Millipore® filter disk, which can be impregnated with growth factors and anti-angiogenic agents in a liquid form prior to Upon subcutaneous administration at body injection. temperature, the Matrigel or Millipore® filter disk forms 15 a solid implant. VEGF embedded in the Matrigel or Millipore® filter disk would be used to recruit vessels within the matrix of the Matrigel or Millipore® filter disk which can be processed histologically for endothelial cell specific vWF (factor VIII antigen) immunohisto-20 chemistry, Trichrome-Masson stain, or hemoglobin content. Like the cornea, the Matrigel or Millipore® filter disk are avascular; however, it is not tissue. In the Matrigel or Millipore® filter disk model, ribozymes are administered within the matrix of the Matrigel or Millipore® 25 filter disk to test their anti-angiogenic efficacy. Thus, delivery issues in this model, as with delivery of ribozymes by Hydron-coated Teflon pellets in the rat cornea model, may be less problematic due to the homogeneous presence of the ribozyme within the respective matrix.

other angiogenic models listed previously. The ability to use VEGF as a pro-angiogenic stimulus in both models is highly desirable since ribozymes will target only VEGFr mRNA. In other words, the involvement of other non-specific types of stimuli in the cornea and Matrigel models is not advantageous from the standpoint of understanding the pharmacologic mechanism by which the

38

anti-VEGFr mRNA ribozymes produce their effects. In addition, the models will allow for testing the specificity of the anti-VEGFr mRNA ribozymes by using either a- or bFGF as a pro-angiogenic factor. Vessel recruitment using FGF 5 should not be affected in either model by anti-VEGFr mRNA ribozymes. Other models of angiogenesis including vessel formation in the female reproductive system using hormonal manipulation (Shweiki et al., 1993 supra); a variety of vascular solid tumor models which involve indirect cor-10 relations with angiogenesis (O'Reilly et al., 1994 supra; Senger et al., 1993 supra; Takahasi et al., 1994 supra; Kim et al., 1993 supra); and retinal neovascularization following transient hypoxia (Pierce et al., 1995 supra) were not selected for efficacy screening due to their 15 non-specific nature, although there is a correlation between VEGF and angiogenesis in these models.

Other model systems to study tumor angiogenesis is reviewed by Folkman, 1985 Adv. Cancer. Res.. 43, 175.

flt-1, KDR and/or flk-1 protein levels can be
measured clinically or experimentally by FACS analysis.
flt-1, KDR and/or flk-1 encoded mRNA levels will be
assessed by Northern analysis, RNase-protection, primer
extension analysis and/or quantitative RT-PCR. Ribozymes
that block flt-1, KDR and/or flk-1 protein encoding mRNAs
and therefore result in decreased levels of flt-1, KDR
and/or flk-1 activity by more than 20% in vitro will be
identified.

Ribozymes and/or genes encoding them are delivered by either free delivery, liposome delivery, cationic lipid delivery, adeno-associated virus vector delivery, adeno-virus vector delivery, retrovirus vector delivery or plasmid vector delivery in these animal model experiments (see above).

Patients can be treated by locally administering nucleic acids targeted against VEGF-R by direct injection. Routes of administration may include, but are not limited to, intravascular, intramuscular, subcutaneous, intra-

39

articular, aerosol inhalation, oral (tablet, capsule or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery.

# 

The purpose of this study was to assess the antiangiogenic activity of hammerhead ribozymes targeted against flt-1 4229 site in the rat cornea model of VEGF induced angiogenesis (see above). These ribozymes have either active or inactive catalytic core and either bind and cleave or just bind to VEGF-R mRNA of the flt-1 subtype. The active ribozymes, that are able to bind and cleave the target RNA, have been shown to inhibit (125I-labeled) VEGF binding in cultured endothelial cells 15 and produce a dose-dependent decrease in VEGF induced endothelial cell proliferation in these Examples 3-5 above). The catalytically inactive forms of these ribozymes, wherein the ribozymes can only bind to the RNA but cannot catalyze RNA cleavage, fail to show 20 these characteristics. The ribozymes and VEGF were co-delivered using the filter disk method: Nitrocellulose filter disks (Millipore®) of 0.057 diameter were immersed in appropriate solutions and were surgically implanted in rat cornea as described by Pandey et al., supra. 25 delivery method has been shown to deliver rhodaminelabeled free ribozyme to scleral cells and, likelihood cells of the pericorneal vascular plexus. Since the active ribozymes show cell culture efficacy and can be delivered to the target site using the disk method, 30 it is essential that these ribozymes be assessed for in vivo anti-angiogenic activity.

The stimulus for angiogenesis in this study was the treatment of the filter disk with 30 mM VEGF which is implanted within the cornea's stroma. This dose yields reproducible neovascularization stemming from the pericorneal vascular plexus growing toward the disk in a

40

dose-response study 5 days following implant. disks treated only with the vehicle for VEGF show no angiogenic response. The ribozymes was co-adminstered with VEGF on a disk in two different ribozyme concen-One concern with the simultaneous adminis-5 trations. tration is that the ribozymes will not be able to inhibit angiogenesis since VEGF receptors can be stimulated. However, we have observed that in low VEGF doses, the neovascular response reverts to normal suggesting that the 10 VEGF stimulus is essential for maintaining the angiogenic response. Blocking the production of VEGF receptors using simultaneous administration of anti-VEGF-R mRNA ribozymes could attenuate the normal neovascularization induced by the filter disk treated with VEGF.

## 15 Materials and Methods:

- 1. Stock hammerhead ribozyme solutions:
  - a. flt-1 4229 (786  $\mu$ M) Active
  - b. flt-1 4229 (736  $\mu$ M) Inactive

#### 2. Experimental solutions/groups:

| 20 | Group 1 | Solution 1 | Control VEGF solution: 30 $\mu M$ in 82mM Tris base  |
|----|---------|------------|--|
|    | Group 2 | Solution 2 | flt-1 4229 (1 $\mu g/\mu L$ ) in 30 $\mu M$ VEGF/82 mM Tris base                             |
| 25 | Group 3 | Solution 3 | flt-1 4229 (10 $\mu \mathrm{g}/\mu \mathrm{L}$ ) in 30 $\mu \mathrm{M}$ VEGF/82 mM Tris base |
|    | Group 4 | Solution 4 | No VEGF, flt-1 4229 (10 $\mu \text{g}/\mu \text{L})$ in 82 mM Tris base                      |
|    | Group 5 | Solution 5 | No VEGF, No ribozyme in 82 mM Tris base  |

30 10 eyes per group, 5 animals (Since they have similar molecular weights, the molar concentrations should be essentially similar).

Each solution (VEGF and RIBOZYMES) were prepared as a 2X solution for 1:1 mixing for final concentrations

41

above, with the exception of solution 1 in which VEGF was 2X and diluted with ribozyme diluent (sterile water).

#### 3. VEGF\_Solutions

The 2X VEGF solution (60  $\mu$ M) was prepared from a stock of 0.82  $\mu$ g/ $\mu$ L in 50 mM Tris base. 200  $\mu$ L of VEGF stock was concentrated by speed vac to a final volume of 60.8  $\mu$ L, for a final concentration of 2.7  $\mu$ g/ $\mu$ L or 60  $\mu$ M. Six 10  $\mu$ L aliquots was prepared for daily mixing. 2X solutions for VEGF and Ribozyme was stored at 4°C until 10 the day of the surgery. Solutions were mixed for each day of surgery. Original 2X solutions was prepared on the day before the first day of the surgery.

## 4. Surgical Solutions:

#### Anesthesia:

stock ketamine hydrochloride 100 mg/mL stock xylazine hydrochloride 20 mg/mL stock acepromazine 10 mg/mL

Final anesthesia solution: 50 mg/mL ketamine, 10 mg/mL xylazine, and 0.5 mg/mL acepromazine 5% povidone iodine for opthalmic surgical wash 2% lidocaine (sterile) for opthalmic administration (2 drops per eye) sterile 0.9% NaCl for opthalmic irrigation

#### 5. Surgical Methods:

20

Standard surgical procedure as described in Pandey et al., supra. Filter disks were incubated in 1  $\mu$ L of each solution for approximately 30 minutes prior to implantation.

# 5. <u>Experimental Protocol:</u>

The animal cornea were treated with the treatment groups as described above. Animals were allowed to recover for 5 days after treatment with daily observation (scoring 0 - 3). On the fifth day animals were euthanized and

42

digital images of each eye was obtained for quantitaion using Image Pro Plus. Quantitated neovascular surface area were analyzed by ANOVA followed by two post-hoc tests including Dunnets and Tukey-Kramer tests for significance at the 95% confidence level. Dunnets provide information on the significance between the differences within the means of treatments vs. controls while Tukey-Kramer provide information on the significance of differences within the means of each group.

Results are graphically represented in Figure 18. As shown in the figure, flt-1 4229 active hammerhead ribozyme at both concentrations was effective at inhibiting angiogenesis while the inactive ribozyme did not show any significant reduction in angiogenesis. A statistically signifiant reduction in neovascular surface area was observed only with active ribozymes. This result clearly shows that the ribozymes are capable of significantly inhibiting angiogenesis in vivo. Specifically, the mechanism of inhibition appears to be by the binding and cleavage of target RNA by ribozymes.

#### Diagnostic uses

Ribozymes of this invention may be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of flt-1, KDR 25 and/or flk-1 RNA in a cell. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and threedimensional structure of the target RNA. By using multiple ribozymes described in this invention, one may nucleotide changes which are important to RNA structure and function in vitro, as well as in cells and Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets

43

may be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combinational therapies (e.g., multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other in vitro uses of ribozymes of this invention are well known in the art, and include detection of the presence of mRNAs associated with flt-1, KDR and/or flk-1 related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

In a specific example, ribozymes which can cleave 15 only wild-type or mutant forms of the target RNA are used for the assay. The first ribozyme is used to identify wild-type RNA present in the sample and the second ribozyme will be used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-20 type and mutant RNA will be cleaved by both ribozymes to demonstrate the relative ribozyme efficiencies in the reactions and the absence of cleavage of the "nontargeted" RNA species. The cleavage products from the synthetic substrates will also serve to generate size markers for the analysis of wild-type and mutant RNAs in Thus each analysis will require the sample population. two ribozymes, two substrates and one unknown sample which will be combined into six reactions. The presence of cleavage products will be determined using an RNAse protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in The expression of mRNA whose protein 35 target cells. product is implicated in the development of the phenotype (i.e., flt-1, KDR and/or flk-1) is adequate to establish

44

risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels will be adequate and will decrease the cost of the initial diagnosis. Higher mutant form to wild-type ratios will be correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

Other embodiments are within the following claims.

45

#### Table I

## Characteristics of Ribozymes

#### Group I Introns

Size: -200 to >1000 nucleotides

5 Requires a U in the target sequence immediately 5' of the cleavage site.

Binds 4-6 nucleotides at 5' side of cleavage site.

Over 75 known members of this class. Found in Tetrahymena thermophila rRNA, fungal mitochondria, chloroplasts, phage

10 T4, blue-green algae, and others.

#### RNAseP RNA (M1 RNA)

Size: -290 to 400 nucleotides

RNA portion of a ribonucleoprotein enzyme. Cleaves tRNA precursors to form mature tRNA.

15 Roughly 10 known members of this group all are bacterial in origin.

#### Hammerhead Ribozyme

Size: ~13 to 40 nucleotides.

Requires the target sequence UH immediately 5' of the 20 cleavage site.

Binds a variable number of nucleotides on both sides of the cleavage site.

14 known members of this class. Found in a number of plant pathogens (virusoids) that use RNA as the infectious

25 agent (Figure 1 and 2)

# Hairpin Ribozyme

Size: ~50 nucleotides.

Requires the target sequence GUC immediately 3' of the cleavage site.

30 Binds 4-6 nucleotides at 5' side of the cleavage site and a variable number to the 3' side of the cleavage site.

Only 3 known member of this class. Found in three plant pathogen (satellite RNAs of the tobacco ringspot virus,

46

arabis mosaic virus and chicory yellow mottle virus) which uses RNA as the infectious agent (Figure 3).

# Hepatitis Delta Virus (HDV) Ribozyme

Size: 50-60 nucleotides (at present)

5 Sequence requirements not fully determined.
Binding sites and structural requirements not fully determined, although no sequences 5' of cleavage site are required.

Only 1 known member of this class. Found in human HDV 10 (Figure 4).

#### Neurospora VS RNA Ribozyme

Size: -144 nucleotides (at present)
Cleavage of target RNAs recently demonstrated.

Sequence requirements not fully determined.

15 Binding sites and structural requirements not fully determined. Only 1 known member of this class. Found in Neurospora VS RNA (Figure 5).

# Table II: Human fltl VEGF Receptor-Hammerhead Ribozyme and Substrate Sequence

| 20 | nt.<br>Posi-<br>tion |          | HH Ri   | • | Subs | trate    |           |          |
|----|----------------------|----------|---------|---|------|----------|-----------|----------|
|    | 10                   | GCCGAGAG | CUGAUGA | x | GAA  | AGUGUCCG | CGGACACUC | CUCUCGGC |
|    | 13                   | GGAGCCGA | CUGAUGA | X | GAA  | AGGAGUGU | ACACUCCUC | UCGGCUCC |
| 25 | 15                   | GAGGAGCC | CUGAUGA | x | GAA  | AGAGGAGU | ACUCCUCUC | GGCUCCUC |
|    | 20                   | CCGGGGAG | CUGAUGA | X | GAA  | AGCCGAGA | UCUCGGCUC | CUCCCCGG |
|    | 23                   | CUGCCGGG | CUGAUGA | x | GAA  | AGGAGCCG | CGGCUCCUC | CCCGGCAG |
|    | 43                   | CCCGCUCC | CUGAUGA | x | GAA  | AGCCGCCG | ceccecuc  | GGAGCGGG |
|    | 54                   | GAGCCCCG | CUGAUGA | x | GAA  | AGCCCGCU | AGCGGGCUC | CGGGGCUC |
| 30 | 62                   | CUGCACCC | CUGAUGA | X | GAA  | AGCCCCGG | CCGGGGCUC | GGGUGCAG |
|    | 97                   | CCCCGGGU | CUGAUGA | X | GAA  | AUCCUCGC | GCGAGGAUU | ACCCGGGG |
|    | 98                   | UCCCCGGG | CUGAUGA | x | GAA  | AAUCCUCG | CGAGGAUUA | CCCGGGGA |

|    | 113 | CAGGAGAC | CUGAUGA | X | GAA | ACCACUUC         | GAAGUGGUU GUCUCCUG |
|----|-----|----------|---------|---|-----|------------------|--------------------|
|    | 116 | AGCCAGGA | CUGAUGA | X | GAA | ACAACCAC         | GUGGUUGUC UCCUGGCU |
|    | 118 | CCAGCCAG | CUGAUGA | X | GAA | AGACAACC         | GGUUGUCUC CUGGCUGG |
|    | 145 | CGCGCCCU | CUGAUGA | X | GAA | AGCGCCCG         | CGGGCGCUC AGGGCGCG |
| 5  | 185 | GGCCGCCA | CUGAUGA | x | GAA | AGUCCGUC         | GACGGACUC UGGCGGCC |
|    | 198 | CGGCCAAC | CUGAUGA | X | GAA | ACCCGGCC         | GGCCGGGUC GUUGGCCG |
|    | 201 | CCCCGGCC | CUGAUGA | X | GAA | ACGACCCG         | CGGGUCGUU GGCCGGGG |
|    | 240 | GUGAGCGC | CUGAUGA | X | GAA | ACGCGGCC         | GGCCGCGUC GCGCUCAC |
|    | 246 | ACCAUGGU | CUGAUGA | X | GAA | AGCGCGAC         | GUCGCGCUC ACCAUGGU |
| 10 | 255 | CAGUAGCU | CUGAUGA | X | gaa | ACCAUGGU         | ACCAUGGUC AGCUACUG |
|    | 260 | UGUCCCAG | CUGAUGA | X | GAA | AGCUGACC         | GGUCAGCUA CUGGGACA |
|    | 276 | CACAGCAG | CUGAUGA | X | GAA | ACCCCGGU         | ACCGGGGUC CUGCUGUG |
|    | 294 | AGACAGCU | CUGAUGA | x | GAA | AGCAGCGC         | GCGCUGCUC AGCUGUCU |
|    | 301 | GAGAAGCA | CUGAUGA | x | GAA | ACAGCUGA         | UCAGCUGUC UGCUUCUC |
| 15 | 306 | CCUGUGAG | CUGAUGA | X | GAA | AGCAGACA         | UGUCUGCUU CUCACAGG |
|    | 307 | UCCUGUGA | CUGAUGA | X | GAA | <b>AAGCAG</b> AC | GUCUGCUUC UCACAGGA |
|    | 309 | GAUCCUGU | CUGAUGA | X | GAA | AGAAGCAG         | CUGCUUCUC ACAGGAUC |
|    | 317 | CUGAACUA | CUGAUGA | X | GAA | AUCCUGUG         | CACAGGAUC UAGUUCAG |
|    | 319 | ACCUGAAC | CUGAUGA | x | GAA | AGAUCCUG         | CAGGAUCUA GUUCAGGU |
| 20 | 322 | UGAACCUG | CUGAUGA | x | GAA | ACUAGAUC         | GAUCUAGUU CAGGUUCA |
|    | 323 | UUGAACCU | CUGAUGA | X | GAA | AACUAGAU         | AUCUAGUUC AGGUUCAA |
|    | 328 | UAAUUUUG | CUGAUGA | X | GAA | ACCUGAAC         | GUUCAGGUU CAAAAUUA |
|    | 329 | UUUAAUUU | CUGAUGA | X | GAA | AACCUGAA         | UUCAGGUUC AAAAUUAA |
|    | 335 | GAUCUUUU | CUGAUGA | X | GAA | AUUUUGAA         | UUCAAAAUU AAAAGAUC |
| 25 | 336 | GGAUCUUU | CUGAUGA | X | GAA | AAUUUUGA         | UCAAAAUUA AAAGAUCC |
|    | 343 | CAGUUCAG | CUGAUGA | x | GAA | AUCUUUUA         | UAAAAGAUC CUGAACUG |
|    | 355 | GCCUUUUA | CUGAUGA | X | GAA | ACUCAGUU         | AACUGAGUU UAAAAGGC |
|    | 356 | UGCCUUUU | CUGAUGA | X | GAA | AACUCAGU         | ACUGAGUUU AAAAGGCA |
|    | 357 | GUGCCUUU | CUGAUGA | X | GAA | AAACUCAG         | CUGAGUUUA AAAGGCAC |
| 30 | 375 | GCUUGCAU | CUGAUGA | X | GAA | AUGUGCUG         | CAGCACAUC AUGCAAGC |
|    | 400 | GCAUUGGA | CUGAUGA | x | GAA | AUGCAGUG         | CACUGCAUC UCCAAUGC |
|    | 402 | CUGCAUUG | CUGAUGA | x | GAA | AGAUGCAG         | CUGCAUCUC CAAUGCAG |
|    | 427 | AGACCAUU | CUGAUGA | x | GAA | AUGGGCUG         | CAGCCCAUA AAUGGUCU |

|    | 434          | CAGGCAAA CUGAUGA X GAA ACCAUUUA | UAAAUGGUC UUUGCCUG |
|----|--------------|---------------------------------|--------------------|
|    | 436          | UUCAGGCA CUGAUGA X GAA AGACCAUU | AAUGGUCUU UGCCUGAA |
|    | 437          | UUUCAGGC CUGAUGA X GAA AAGACCAU | AUGGUCUUU GCCUGAAA |
|    | 454          | GCUUUCCU CUGAUGA X GAA ACUCACCA | UGGUGAGUA AGGAAAGC |
| 5  | 477          | GAUUUAGU CUGAUGA X GAA AUGCUCAG | CUGAGCAUA ACUAAAUC |
|    | 481          | GGCAGAUU CUGAUGA X GAA AGUUAUGC | GCAUAACUA AAUCUGCC |
|    | 485          | CACAGGCA CUGAUGA X GAA AUUUAGUU | AACUAAAUC UGCCUGUG |
|    | 512          | UACUGCAG CUGAUGA X GAA AUUGUUUG | CAAACAAUU CUGCAGUA |
|    | <b>51</b> 3  | GUACUGCA CUGAUGA X GAA AAUUGUUU | AAACAAUUC UGCAGUAC |
| 10 | 520          | GGUUAAAG CUGAUGA X GAA ACUGCAGA | UCUGCAGUA CUUUAACC |
|    | 523          | CAAGGUUA CUGAUGA X GAA AGUACUGC | GCAGUACUU UAACCUUG |
|    | 524          | UCAAGGUU CUGAUGA X GAA AAGUACUG | CAGUACUUU AACCUUGA |
|    | <b>52</b> 5  | UUCAAGGU CUGAUGA X GAA AAAGUACU | AGUACUUUA ACCUUGAA |
|    | 530          | CUGUGUUC CUGAUGA X GAA AGGUUAAA | UUUAACCUU GAACACAG |
| 15 | 541          | GUUUGCUU CUGAUGA X GAA AGCUGUGU | ACACAGCUC AAGCAAAC |
|    | 560          | AGCUGUAG CUGAUGA X GAA AGCCAGUG | CACUGGCUU CUACAGCU |
|    | 561          | CAGCUGUA CUGAUGA X GAA AAGCCAGU | ACUGGCUUC UACAGCUG |
|    | 563          | UGCAGCUG CUGAUGA X GAA AGAAGCCA | UGGCUUCUA CAGCUGCA |
|    | 575          | CAGCUAGA CUGAUGA X GAA AUUUGCAG | CUGCAAAUA UCUAGCUG |
| 20 | 5 <b>7</b> 7 | UACAGCUA CUGAUGA X GAA AUAUUUGC | GCAAAUAUC UAGCUGUA |
|    | 579          | GGUACAGC CUGAUGA X GAA AGAUAUUU | AAAUAUCUA GCUGUACC |
|    | 585          | GAAGUAGG CUGAUGA X GAA ACAGCUAG | CUAGCUGUA CCUACUUC |
|    | 589          | CUUUGAAG CUGAUGA X GAA AGGUACAG | CUGUACCUA CUUCAAAG |
|    | 592          | CUUCUUUG CUGAUGA X GAA AGUAGGUA | UACCUACUU CAAAGAAG |
| 25 | 593          | UCUUCUUU CUGAUGA X GAA AAGUAGGU | ACCUACUUC AAAGAAGA |
|    | 614          | AGAUUGCA CUGAUGA X GAA AUUCUGUU | AACAGAAUC UGCAAUCU |
|    | 621          | AAUAUAUA CUGAUGA X GAA AUUGCAGA | UCUGCAAUC UAUAUAUU |
|    | 623          | UAAAUAUA CUGAUGA X GAA AGAUUGCA | UGCAAUCUA UAUAUUUA |
|    | 625          | AAUAAAUA CUGAUGA X GAA AUAGAUUG | CAAUCUAUA UAUUUAUU |
| 30 | 627          | CUAAUAAA CUGAUGA X GAA AUAUAGAU | AUCUAUAUA UUUAUUAG |
|    | 629          | CACUAAUA CUGAUGA X GAA AUAUAUAG | CUAUAUAUU UAUUAGUG |
|    | 630          | UCACUAAU CUGAUGA X GAA AAUAUAUA | UAUAUAUUU AUUAGUGA |
|    | 631          | AUCACUAA CUGAUGA X GAA AAAUAUAU | AUAUAUUUA UUAGUGAU |

|    | 633         | GUAUCACU CUGAUGA X GAA AUAAAUAU | AUAUUUAUU AGUGAUAC |
|----|-------------|---------------------------------|--------------------|
|    | 634         | UGUAUCAC CUGAUGA X GAA AAUAAAUA | UAUUUAUUA GUGAUACA |
|    | 640         | UCUACCUG CUGAUGA X GAA AUCACUAA | UUAGUGAUA CAGGUAGA |
|    | 646         | GAAAGGUC CUGAUGA X GAA ACCUGUAU | AUACAGGUA GACCUUUC |
| 5  | 652         | CUCUACGA CUGAUGA X GAA AGGUCUAC | GUAGACCUU UCGUAGAG |
|    | 653         | UCUCUACG CUGAUGA X GAA AAGGUCUA | UAGACCUUU CGUAGAGA |
|    | 654         | AUCUCUAC CUGAUGA X GAA AAAGGUCU | AGACCUUUC GUAGAGAU |
|    | 657         | UACAUCUC CUGAUGA X GAA ACGAAAGG | CCUUUCGUA GAGAUGUA |
|    | 665         | UUUCACUG CUGAUGA X GAA ACAUCUCU | AGAGAUGUA CAGUGAAA |
| 10 | 675         | AUUUCGGG CUGAUGA X GAA AUUUCACU | AGUGAAAUC CCCGAAAU |
|    | 684         | AUGUGUAU CUGAUGA X GAA AUUUCGGG | CCCGAAAUU AUACACAU |
|    | 685         | CAUGUGUA CUGAUGA X GAA AAUUUCGG | CCGAAAUUA UACACAUG |
|    | 687         | GUCAUGUG CUGAUGA X GAA AUAAUUUC | GAAAUUAUA CACAUGAC |
|    | 711         | GGAAUGAC CUGAUGA X GAA AGCUCCCU | AGGGAGCUC GUCAUUCC |
| 15 | 714         | CAGGGAAU CUGAUGA X GAA ACGAGCUC | GAGCUCGUC AUUCCCUG |
|    | 717         | CGGCAGGG CUGAUGA X GAA AUGACGAG | CUCGUCAUU CCCUGCCG |
|    | 718         | CCGGCAGG CUGAUGA X GAA AAUGACGA | UCGUCAUUC CCUGCCGG |
|    | 729         | GGUGACGU CUGAUGA X GAA ACCCGGCA | UGCCGGGUU ACGUCACC |
|    | 730         | AGGUGACG CUGAUGA X GAA AACCCGGC | GCCGGGUUA CGUCACCU |
| 20 | 734         | UGUUAGGU CUGAUGA X GAA ACGUAACC | GGUUACGUC ACCUAACA |
|    | 739         | AGUGAUGU CUGAUGA X GAA AGGUGACG | CGUCACCUA ACAUCACU |
|    | 744         | GUAACAGU CUGAUGA X GAA AUGUUAGG | CCUAACAUC ACUGUUAC |
|    | 750         | UUUAAAGU CUGAUGA X GAA ACAGUGAU | AUCACUGUU ACUUUAAA |
|    | 751         | UUUUAAAG CUGAUGA X GAA AACAGUGA | UCACUGUUA CUUUAAAA |
| 25 | 754         | CUUUUUUA CUGAUGA X GAA AGUAACAG | CUGUUACUU UAAAAAAG |
|    | <b>75</b> 5 | ACUUUUUU CUGAUGA X GAA AAGUAACA | UGUUACUUU AAAAAAGU |
|    | 756         | AACUUUUU CUGAUGA X GAA AAAGUAAC | GUUACUUUA AAAAAGUU |
|    | 764         | CAAGUGGA CUGAUGA X GAA ACUUUUUU | AAAAAAGUU UCCACUUG |
|    | 765         | UCAAGUGG CUGAUGA X GAA AACUUUUU | AAAAAGUUU CCACUUGA |
| 30 | 766         | GUCAAGUG CUGAUGA X GAA AAACUUUU | AAAAGUUUC CACUUGAC |
|    | 771         | AAAGUGUC CUGAUGA X GAA AGUGGAAA | UUUCCACUU GACACUUU |
|    | 778         | AGGGAUCA CUGAUGA X GAA AGUGUCAA | UUGACACUU UGAUCCCU |
|    | 779         | CAGGGAUC CUGAUGA X GAA AAGUGUCA | UGACACUUU GAUCCCUG |

|    | 783         | CCAUCAGG | CUGAUGA | X | GAA | AUCAAAGU | ACUUUGAUC | CCUGAUGG |
|----|-------------|----------|---------|---|-----|----------|-----------|----------|
|    | 801         | UCCCAGAU | CUGAUGA | X | GAA | AUGCGUUU | AAACGCAUA | AUCUGGGA |
|    | 804         | CUGUCCCA | CUGAUGA | X | GAA | AUUAUGCG | CGCAUAAUC | UGGGACAG |
|    | 814         | GCCCUUUC | CUGAUGA | X | GAA | ACUGUCCC | GGGACAGUA | GAAAGGGC |
| 5  | 824         | AUAUGAUG | CUGAUGA | X | GAA | AGCCCUUU | AAAGGGCUU | CAUCAUAU |
|    | 825         | GAUAUGAU | CUGAUGA | X | GAA | AAGCCCUU | AAGGGCUUC | AUCAUAUC |
|    | 828         | UUUGAUAU | CUGAUGA | X | GAA | AUGAAGCC | GGCUUCAUC | AUAUCAAA |
|    | 831         | GCAUUUGA | CUGAUGA | X | GAA | AUGAUGAA | UUCAUCAUA | UCAAAUGC |
|    | ·833        | UUGCAUUU | CUGAUGA | X | GAA | AUAUGAUG | CAUCAUAUC | AAAUGCAA |
| 10 | 845         | UUUCUUUG | CUGAUGA | X | GAA | ACGUUGCA | UGCAACGUA | CAAAGAAA |
|    | 855         | AGAAGCCC | CUGAUGA | X | GAA | AUUUCUUU | AAAGAAAUA | GGGCUUCU |
|    | 861         | CAGGUCAG | CUGAUGA | X | GAA | AGCCCUAU | AUAGGGCUU | CUGACCUG |
|    | 862         | ACAGGUCA | CUGAUGA | x | GAA | AAGCCCUA | UAGGGCUUC | UGACCUGU |
|    | 882         | UGCCCAUU | CUGAUGA | x | GAA | ACUGUUGC | GCAACAGUC | AAUGGGCA |
| 15 | 892         | CUUAUACA | CUGAUGA | X | GAA | AUGCCCAU | AUGGGCAUU | UGUAUAAG |
|    | 893         | UCUUAUAC | CUGAUGA | X | GAA | AAUGCCCA | UGGGCAUUU | GUAUAAGA |
|    | 896         | UUGUCUUA | CUGAUGA | X | GAA | ACAAAUGC | GCAUUUGUA | UAAGACAA |
|    | 898         | GUUUGUCU | CUGAUGA | X | GAA | AUACAAAU | AUUUGUAUA | AGACAAAC |
|    | 908         | GUGUGAGA | CUGAUGA | x | GAA | AGUUUGUC | GACAAACUA | UCUCACAC |
| 20 | 910         | AUGUGUGA | CUGAUGA | X | GAA | AUAGUUUG | CAAACUAUC | UCACACAU |
|    | 912         | CGAUGUGU | CUGAUGA | X | GAA | AGAUAGUU | AACUAUCUC | ACACAUCG |
|    | 919         | GGUUUGUC | CUGAUGA | x | GAA | AUGUGUGA | UCACACAUC | GACAAACC |
|    | 931         | UAUGAUUG | CUGAUGA | X | GAA | AUUGGUUU | AAACCAAUA | CAAUCAUA |
|    | 936         | ACAUCUAU | CUGAUGA | X | GAA | AUUGUAUU | AAUACAAUC | AUAGAUGU |
| 25 | 939         | UGGACAUC | CUGAUGA | x | GAA | AUGAUUGU | ACAAUCAUA | GAUGUCCA |
|    | 945         | CUUAUUUG | CUGAUGA | X | GAA | ACAUCUAU | AUAGAUGUC | CAAAUAAG |
|    | 951         | GGUGUGCU | CUGAUGA | X | GAA | AUUUGGAC | GUCCAAAUA | AGCACACC |
|    | 969         | AGUAAUUU | CUGAUGA | X | GAA | ACUGGGCG | CGCCCAGUC | AAAUUACU |
|    | 974         | CUCUAAGU | CUGAUGA | X | GAA | AUUUGACU | AGUCAAAUU | ACUUAGAG |
| 30 | 975         | CCUCUAAG | CUGAUGA | X | GAA | AAUUUGAC | GUCAAAUUA | CUUAGAGG |
|    | 978         | UGGCCUCU | CUGAUGA | X | GAA | AGUAAUUU | AAAUUACUU | AGAGGCCA |
|    | <b>97</b> 9 | AUGGCCUC | CUGAUGA | x | GAA | AAGUAAUU | AAUUACUUA | GAGGCCAU |
|    | 988         | GACAAGAG | CUGAUGA | x | GAA | AUGGCCUC | GAGGCCAUA | CUCUUGUC |

|    | 991  | GAGGACAA | CUGAUGA | X   | GAA | AGUAUGGC | GCCAUACUC | י יייסטככטכ |
|----|------|----------|---------|-----|-----|----------|-----------|-------------|
|    | 993  | UUGAGGAC | CUGAUGA | X   | GAA | AGAGUAUG | CAUACUCUU | GUCCUCAA    |
|    | 996  | CAAUUGAG | CUGAUGA | X   | GAA | ACAAGAGU | ACUCUUGUC | CUCAAUUG    |
|    | 999  | GUACAAUU | CUGAUGA | . x | GAA | AGGACAAG | cuuguccuc | AAUUGUAC    |
| 5  | 1003 | AGCAGUAC | CUGAUGA | . x | GAA | AUUGAGGA | UCCUCAAUU | GUACUGCU    |
|    | 1006 | GGUAGCAG | CUGAUGA | x   | GAA | ACAAUUGA | UCAAUUGUA | CUGCUACC    |
|    | 1012 | GGGAGUGG | CUGAUGA | x   | GAA | AGCAGUAC | GUACUGCUA | CCACUCCC    |
|    | 1018 | GUUCAAGG | CUGAUGA | X   | GAA | AGUGGUAG | CUACCACUC | CCUUGAAC    |
|    | 1022 | UCGUGUUC | CUGAUGA | x   | GAA | AGGGAGUG | CACUCCCUU | GAACACGA    |
| 10 | 1035 | GUCAUUUG | CUGAUGA | x   | GAA | ACUCUCGU | ACGAGAGUU | CAAAUGAC    |
|    | 1036 | GGUCAUUU | CUGAUGA | x   | GAA | AACUCUCG | CGAGAGUUC | AAAUGACC    |
|    | 1051 | AUCAGGGU | CUGAUGA | x   | GAA | ACUCCAGG | CCUGGAGUU | ACCCUGAU    |
|    | 1052 | CAUCAGGG | CUGAUGA | x   | GAA | AACUCCAG | CUGGAGUUA | CCCUGAUG    |
|    | 1069 | AGCUCUCU | CUGAUGA | X   | GAA | UUUUUUUA | AAAAAAUA  | AGAGAGCU    |
| 15 | 1078 | CCUUACGG | CUGAUGA | x   | GAA | AGCUCUCU | AGAGAGCUU | CCGUAAGG    |
|    | 1079 | GCCUUACG | CUGAUGA | x   | GAA | AAGCUCUC | GAGAGCUUC | CGUAAGGC    |
|    | 1083 | CGUCGCCU | CUGAUGA | X   | GAA | ACGGAAGC | GCUUCCGUA | AGGCGACG    |
|    | 1095 | CUUUGGUC | CUGAUGA | x   | GAA | AUUCGUCG | CGACGAAUU | GACCAAAG    |
|    | 1108 | GGCAUGGG | CUGAUGA | x   | GAA | AUUGCUUU | AAAGCAAUU | CCCAUGCC    |
| 20 | 1109 | UGGCAUGG | CUGAUGA | x   | GAA | AAUUGCUU | AAGCAAUUC | CCAUGCCA    |
|    | 1122 | CUGUAGAA | CUGAUGA | X   | GAA | AUGUUGGC | GCCAACAUA | UUCUACAG    |
|    | 1124 | CACUGUAG | CUGAUGA | X   | GAA | AUAUGUUG | CAACAUAUU | CUACAGUG    |
|    | 1125 | ACACUGUA | CUGAUGA | X   | GAA | AAUAUGUU | AACAUAUUC | UACAGUGU    |
|    | 1127 | GAACACUG | CUGAUGA | X   | GAA | AGAAUAUG | CAUAUUCUA | CAGUGUUC    |
| 25 | 1134 | AUAGUAAG | CUGAUGA | X   | GAA | ACACUGUA | UACAGUGUU | CUUACUAU    |
|    | 1135 | AAUAGUAA | CUGAUGA | x   | GAA | AACACUGU | ACAGUGUUC | UUACUAUU    |
|    | 1137 | UCAAUAGU | CUGAUGA | x   | GAA | AGAACACU | AGUGUUCUU | ACUAUUGA    |
|    | 1138 | GUCAAUAG | CUGAUGA | x   | GAA | AAGAACAC | GUGUUCUUA | CUAUUGAC    |
|    | 1141 | UUUGUCAA | CUGAUGA | x   | GAA | AGUAAGAA | UUCUUACUA | UUGACAAA    |
| 30 | 1143 | AUUUUGUC | CUGAUGA | X   | GAA | AUAGUAAG | CUUACUAUU | GACAAAAU    |
|    | 1173 | CAAGUAUA | CUGAUGA | X   | GAA | AGUCCUUU | AAAGGACUU | UAUACUUG    |
|    | 1174 | ACAAGUAU | CUGAUGA | X   | GAA | AAGUCCUU | AAGGACUUU | AUACUUGU    |
|    | 1175 | GACAAGUA | CUGAUGA | X   | GAA | AAAGUCCU | AGGACUUUA | UACUUGUC    |
|    |      |          |         |     |     |          |           |             |

|    | 1177 | ACGACAA  | G CUGAUG  | <b>A</b> : | X GA | A AUAAAGUC | GACUUUAUA CUUGUCGU   |
|----|------|----------|-----------|------------|------|------------|--|
|    | 1180 | UACACGA  | C CUGAUG  | A :        | K GA | A AGUAUAAA | UUUAUACUU GUCGUGUA   |
|    | 1183 | CCUUACA  | CUGAUG    | <b>X</b> 2 | K GA | A ACAAGUAU | AUACUUGUC GUGUAAGG   |
|    | 1188 | CCACUCCI | J CUGAUG! |            | ( GA | A ACACGACA | UGUCGUGUA AGGAGUGG   |
| 5  | 1202 | AUUUGAA  | J CUGAUG  |            | ( GA | A AUGGUCCA | UGGACCAUC AUUCAAAU   |
|    | 1205 | CAGAUUU  | G CUGAUGA | . 3        | GA   | A AUGAUGGU | ACCAUCAUU CAAAUCUG   |
| •  | 1206 | ACAGAUUT | J CUGAUGA |            | GAZ  | AAUGAUGG   | CCAUCAUUC AAAUCUGU   |
|    | 1211 | UGUUAACA | CUGAUGA   | . X        | GAZ  | AUUUGAAU   | AUUCAAAUC UGUUAACA   |
|    | 1215 | GAGGUGUU | J CUGAUGA | X          | GAA  | ACAGAUUU   | AAAUCUGUU AACACCUC   |
| 10 | 1216 | UGAGGUGU | CUGAUGA   | X          | GAA  | AACAGAUU   | AAUCUGUUA ACACCUCA   |
|    | 1223 | UAUGCACU | CUGAUGA   | X          | GAA  | AGGUGUUA   | UAACACCUC AGUGCAUA   |
|    | 1231 | AUCAUAUA | CUGAUGA   | X          | GAA  | AUGCACUG   | CAGUGCAUA UAUAUGAU   |
|    | 1233 | UUAUCAUA | CUGAUGA   | X          | GAA  | AUAUGCAC   | GUGCAUAUA UAUGAUAA   |
|    | 1235 | CUUUAUCA | CUGAUGA   | X          | GAA  | AUAUAUGC   | GCAUAUAUA UGAUAAAG   |
| 15 | 1240 | GAAUGCUU | CUGAUGA   | X          | GAA  | AUCAUAUA   | UAUAUGAUA AAGCAUUC   |
|    | 1247 | CAGUGAUG | CUGAUGA   | X          | GAA  | AUGCUUUA   | UAAAGCAUU CAUCACUG   |
|    | 1248 | ACAGUGAU | CUGAUGA   | X          | GAA  | AAUGCUUU   | AAAGCAUUC AUCACUGU   |
|    | 1251 | UUCACAGU | CUGAUGA   | X          | GAA  | AUGAAUGC   | GCAUUCAUC ACUGUGAA   |
|    | 1264 | CUGUUUUC | CUGAUGA   | X          | GAA  | AUGUUUCA   | UGAAACAUC GAAAACAG   |
| 20 | 1281 | ACGGUUUC | CUGAUGA   | X          | GAA  | AGCACCUG   | CAGGUGCUU GAAACCGU   |
|    | 1290 | UUGCCAGC | CUGAUGA   | X          | GAA  | ACGGUUUC   | GAAACCGUA GCUGGCAA   |
|    | 1304 | GCCGGUAA | CUGAUGA   | X          | GAA  | ACCGCUUG   | CAAGCGGUC UUACCGGC   |
|    | 1306 | GAGCCGGU | CUGAUGA   | X          | GAA  | AGACCGCU   | AGCGGUCUU ACCGGCUC   |
|    | 1307 | AGAGCCGG | CUGAUGA   | X          | GAA  | AAGACCGC   | GCGGUCUUA CCGGCUCU   |
| 25 | 1314 | UUCAUAGA |           |            |      |            | UACCGGCUC UCUAUGAA   |
|    | 1316 | CUUUCAUA |           |            |      |            | CCGGCUCUC UAUGAAAG   |
|    | 1318 | CACUUUCA |           |            |      |            | GGCUCUCUA UGAAAGUG   |
|    | 1334 | GCGAGGGA |           |            |      |            | GAAGGCAUU UCCCUCGC   |
|    | 1335 |          |           |            |      | AAUGCCUU   | AAGGCAUUU CCCUCGCC   |
| 30 | 1336 |          |           |            |      |            | AGGCAUUUC CCUCGCCG   |
|    | 1340 |          |           |            |      | AGGGAAAU   | The state of the s |
|    | 1350 |          |           |            |      |            | CCGGAAGUU GUAUGGUU   |
|    | 1353 | UUUAACCA | CUGAUGA   | х          | GAA  | ACAACUUC   | GAAGIIIGIIA IIGGIIIAAA   |

|    | 1358 | CAUCUUUU | CUGAUGA | X   | GAA | ACCAUACA | UGUAUGGUU AAAAGAUG |
|----|------|----------|---------|-----|-----|----------|--------------------|
|    | 1359 | CCAUCUUU | CUGAUGA | X   | GAA | AACCAUAC | GUAUGGUUA AAAGAUGG |
|    | 1370 | UCGCAGGU | CUGAUGA | . x | GAA | ACCCAUCU | AGAUGGGUU ACCUGCGA |
|    | 1371 | GUCGCAGG | CUGAUGA | X   | GAA | AACCCAUC | GAUGGGUUA CCUGCGAC |
| 5  | 1388 | AGCGAGCA | CUGAUGA | X   | GAA | AUUUCUCA | UGAGAAAUC UGCUCGCU |
|    | 1393 | CAAAUAGC | CUGAUGA | X   | GAA | AGCAGAUU | AAUCUGCUC GCUAUUUG |
|    | 1397 | GAGUCAAA | CUGAUGA | X   | GAA | AGCGAGCA | UGCUCGCUA UUUGACUC |
|    | 1399 | ACGAGUCA | CUGAUGA | X   | GAA | AUAGCGAG | CUCGCUAUU UGACUCGU |
|    | 1400 | CACGAGUC | CUGAUGA | X   | GAA | AAUAGCGA | UCGCUAUUU GACUCGUG |
| 10 | 1405 | GUAGCCAC | CUGAUGA | X   | GAA | AGUCAAAU | AUUUGACUC GUGGCUAC |
|    | 1412 | UUAACGAG | CUGAUGA | X   | GAA | AGCCACGA | UCGUGGCUA CUCGUUAA |
|    | 1415 | UAAUUAAC | CUGAUGA | X   | GAA | AGUAGCCA | UGGCUACUC GUUAAUUA |
|    | 1418 | UGAUAAUU | CUGAUGA | X   | GAA | ACGAGUAG | CUACUCGUU AAUUAUCA |
|    | 1419 | UUGAUAAU | CUGAUGA | X   | GAA | AACGAGUA | UACUCGUUA AUUAUCAA |
| 15 | 1422 | UCCUUGAU | CUGAUGA | X   | GAA | AUUAACGA | UCGUUAAUU AUCAAGGA |
|    | 1423 | GUCCUUGA | (AGAUGA | X   | GAA | AAUUAACG | CGUUAAUUA UCAAGGAC |
|    | 1425 | ACGUCCUU | CUGAUGA | X   | GAA | AUAAUUAA | UUAAUUAUC AAGGACGU |
|    | 1434 | UCUUCAGU | CUGAUGA | x   | GAA | ACGUCCUU | AAGGACGUA ACUGAAGA |
|    | 1456 | GAUUGUAU | CUGAUGA | X   | GAA | AUUCCCUG | CAGGGAAUU AUACAAUC |
| 20 | 1457 | AGAUUGUA | CUGAUGA | x   | GAA | AAUUCCCU | AGGGAAUUA UACAAUCU |
|    | 1459 | CAAGAUUG | CUGAUGA | X   | GAA | AUAAUUCC | GGAAUUAUA CAAUCUUG |
|    | 1464 | CUCAGCAA | CUGAUGA | X   | GAA | AUUGUAUA | UAUACAAUC UUGCUGAG |
|    | 1466 | UGCUCAGC | CUGAUGA | X   | GAA | AGAUUGUA | UACAAUCUU GCUGAGCA |
|    | 1476 | GACUGUUU | CUGAUGA | X   | GAA | AUGCUCAG | CUGAGCAUA AAACAGUC |
| 25 | 1484 | ACACAUUU | CUGAUGA | X   | GAA | ACUGUUUU | AAAACAGUC AAAUGUGU |
|    | 1493 | GGUUUUUA | CUGAUGA | X   | GAA | ACACAUUU | AAAUGUGUU UAAAAACC |
|    | 1494 | AGGUUUUU | CUGAUGA | X   | GAA | AACACAUU | AAUGUGUUU AAAAACCU |
|    | 1495 | GAGGUUUU | CUGAUGA | X   | GAA | AAACACAU | AUGUGUUUA AAAACCUC |
|    | 1503 | GUGGCAGU | CUGAUGA | X   | GAA | AGGUUUUU | AAAAACCUC ACUGCCAC |
| 30 | 1513 | GACAAUUA | CUGAUGA | X   | GAA | AGUGGCAG | CUGCCACUC UAAUUGUC |
|    | 1515 | UUGACAAU | CUGAUGA | X   | GAA | AGAGUGGC | GCCACUCUA AUUGUCAA |
|    | 1518 | ACAUUGAC | CUGAUGA | X   | GAA | AUUAGAGU | ACUCUAAUU GUCAAUGU |
|    | 1521 | UUCACAUU | CUGAUGA | x   | GAA | ACAAUUAG | CUAAUUGUC AAUGUGAA |

|    | 1539         | UUUUCGUA CUGAUGA X GAA AUCUGGGG | CCCCAGAUU UACGAAAA |
|----|--------------|---------------------------------|--------------------|
|    | 1540         | CUUUUCGU CUGAUGA X GAA AAUCUGGG | CCCAGAUUU ACGAAAAG |
|    | 1541         | CCUUUUCG CUGAUGA X GAA AAAUCUGG | CCAGAUUUA CGAAAAGG |
|    | 1556         | GAAACGAU CUGAUGA X GAA ACACGGCC | GGCCGUGUC AUCGUUUC |
| 5  | 1559         | CUGGAAAC CUGAUGA X GAA AUGACACG | CGUGUCAUC GUUUCCAG |
|    | 1562         | GGUCUGGA CUGAUGA X GAA ACGAUGAC | GUCAUCGUU UCCAGACC |
|    | <b>156</b> 3 | GGGUCUGG CUGAUGA X GAA AACGAUGA | UCAUCGUUU CCAGACCC |
|    | 1564         | CGGGUCUG CUGAUGA X GAA AAACGAUG | CAUCGUUUC CAGACCCG |
|    | 1576         | UGGGUAGA CUGAUGA X GAA AGCCGGGU | ACCCGGCUC UCUACCCA |
| 10 | 1578         | AGUGGGUA CUGAUGA X GAA AGAGCCGG | CCGGCUCUC UACCCACU |
|    | 1580         | CCAGUGGG CUGAUGA X GAA AGAGAGCC | GGCUCUCUA CCCACUGG |
|    | 1602         | CAAGUCAG CUGAUGA X GAA AUUUGUCU | AGACAAAUC CUGACUUG |
|    | 1609         | UGCGGUAC CUGAUGA X GAA AGUCAGGA | UCCUGACUU GUACCGCA |
|    | 1612         | AUAUGCGG CUGAUGA X GAA ACAAGUCA | UGACUUGUA CCGCAUAU |
| 15 | 1619         | GGAUACCA CUGAUGA X GAA AUGCGGUA | UACCGCAUA UGGUAUCC |
|    | 1624         | UUGAGGGA CUGAUGA X GAA ACCAUAUG | CAUAUGGUA UCCCUCAA |
|    | 1626         | GGUUGAGG CUGAUGA X GAA AUACCAUA | UAUGGUAUC CCUCAACC |
|    | 1630         | UGUAGGUU CUGAUGA X GAA AGGGAUAC | GUAUCCCUC AACCUACA |
|    | 1636         | CUUGAUUG CUGAUGA X GAA AGGUUGAG | CUCAACCUA CAAUCAAG |
| 20 | 1641         | AACCACUU CUGAUGA X GAA AUUGUAGG | CCUACAAUC AAGUGGUU |
|    | 1649         | GGUGCCAG CUGAUGA X GAA ACCACUUG | CAAGUGGUU CUGGCACC |
|    | 1650         | GGGUGCCA CUGAUGA X GAA AACCACUU | AAGUGGUUC UGGCACCC |
|    | 1663         | AUUAUGGU CUGAUGA X GAA ACAGGGGU | ACCCCUGUA ACCAUAAU |
|    | 1669         | GGAAUGAU CUGAUGA X GAA AUGGUUAC | GUAACCAUA AUCAUUCC |
| 25 | 1672         | UUCGGAAU CUGAUGA X GAA AUUAUGGU | ACCAUAAUC AUUCCGAA |
|    | 1675         | UGCUUCGG CUGAUGA X GAA AUGAUUAU | AUAAUCAUU CCGAAGCA |
|    |              | UUGCUUCG CUGAUGA X GAA AAUGAUUA | UAAUCAUUC CGAAGCAA |
|    | 1694         | UGGAACAA CUGAUGA X GAA AGUCACAC | GUGUGACUU UUGUUCCA |
|    | 1695         | UUGGAACA CUGAUGA X GAA AAGUCACA | UGUGACUUU UGUUCCAA |
| 30 | 1696         | AUUGGAAC CUGAÙGA X GAA AAAGUCAC | GUGACUUUU GUUCCAAU |
|    | 1699         | AUUAUUGG CUGAUGA X GAA ACAAAAGU | ACUUUUGUU CCAAUAAU |
|    | 1700         | CAUUAUUG CUGAUGA X GAA AACAAAAG | CUUUUGUUC CAAUAAUG |
|    | 1705         | CUCUUCAU CUGAUGA X GAA AUUGGAAC | GUUCCAAUA AUGAAGAG |

|    |      |          | <i>@</i> 101101 | •          |     |          |                    |
|----|------|----------|-----------------|------------|-----|----------|--------------------|
|    | 1715 |          |                 |            |     | ACUCUUCA | UGAAGAGUC CUUUAUCC |
|    | 1718 | CCAGGAUA | CUGAUGA         | . х        | GAA | AGGACUCU | AGAGUCCUU UAUCCUGG |
|    | 1719 | UCCAGGAU | CUGAUGA         | . х        | GAA | AAGGACUC | GAGUCCUUU AUCCUGGA |
|    | 1720 | AUCCAGGA | CUGAUGA         | . <b>X</b> | GAA | AAAGGACU | AGUCCUUUA UCCUGGAU |
| 5  | 1722 | GCAUCCAG | CUGAUGA         | X          | GAA | AUAAAGGA | UCCUUUAUC CUGGAUGC |
|    | 1755 | AUGCUCUC | CUGAUGA         | X          | GAA | AUUCUGUU | AACAGAAUU GAGAGCAU |
|    | 1764 | CGCUGAGU | CUGAUGA         | X          | GAA | AUGCUCUC | GAGAGCAUC ACUCAGCG |
|    | 1768 | CAUGCGCU | CUGAUGA         | X          | GAA | AGUGAUGC | GCAUCACUC AGCGCAUG |
|    | 1782 | CCUUCUAU | CUGAUGA         | X          | GAA | AUUGCCAU | AUGGCAAUA AUAGAAGG |
| 10 | 1785 | UUUCCUUC | CUGAUGA         | x          | GAA | AUUAUUGC | GCAAUAAUA GAAGGAAA |
|    | 1798 | AGCCAUCU | CUGAUGA         | x          | GAA | AUUCUUUC | GAAAGAAUA AGAUGGCU |
|    | 1807 | CAAGGUGC | CUGAUGA         | x          | GAA | AGCCAUCU | AGAUGGCUA GCACCUUG |
|    | 1814 | CCACAACC | CUGAUGA         | x          | GAA | AGGUGCUA | UAGCACCUU GGUUGUGG |
|    | 1818 | UCAGCCAC | CUGAUGA         | x          | GAA | ACCAAGGU | ACCUUGGUU GUGGCUGA |
| 15 | 1829 | AAAUUCUA | CUGAUGA         | x          | GAA | AGUCAGCC | GGCUGACUC UAGAAUUU |
|    | 1831 | AGAAAUUC | CUGAUGA         | x          | GAA | AGAGUCAG | CUGACUCUA GAAUUUCU |
|    | 1836 | AUUCCAGA | CUGAUGA         | x          | GAA | AUUCUAGA | UCUAGAAUU UCUGGAAU |
|    | 1837 | GAUUCCAG | CUGAUGA         | x          | GAA | AAUUCUAG | CUAGAAUUU CUGGAAUC |
|    | 1838 | AGAUUCCA | CUGAUGA         | X          | GAA | AAAUUCUA | UAGAAUUUC UGGAAUCU |
| 20 | 1845 | CAAAUGUA | CUGAUGA         | x          | GAA | AUUCCAGA | UCUGGAAUC UACAUUUG |
|    | 1847 | UGCAAAUG | CUGAUGA         | X          | GAA | AGAUUCCA | UGGAAUCUA CAUUUGCA |
|    | 1851 | GCUAUGCA | CUGAUGA         | x          | GAA | AUGUAGAU | AUCUACAUU UGCAUAGC |
|    | 1852 | AGCUAUGC | CUGAUGA         | x          | GAA | AAUGUAGA | UCUACAUUU GCAUAGCU |
|    | 1857 | UUGGAAGC | CUGAUGA         | x          | GAA | AUGCAAAU | AUUUGCAUA GCUUCCAA |
| 25 | 1861 | UUUAUUGG | CUGAUGA         | x          | GAA | AGCUAUGC | GCAUAGCUU CCAAUAAA |
|    | 1862 | CUUUAUUG | CUGAUGA         | x          | GAA | AAGCUAUG | CAUAGCUUC CAAUAAAG |
|    | 1867 | CCCAACUU | CUGAUGA         | x          | GAA | AUUGGAAG | CUUCCAAUA AAGUUGGG |
|    | 1872 | ACAGUCCC | CUGAUGA         | x          | GAA | ACUUUAUU | AAUAAAGUU GGGACUGU |
|    | 1893 | UAAAAGCU | CUGAUGA         | x          | GAA | AUGUUUCU | AGAAACAUA AGCUUUUA |
| 30 | 1898 | UGAUAUAA | CUGAUGA         | x          | GAA | AGCUUAUG | CAUAAGCUU UUAUAUCA |
|    | 1899 | GUGAUAUA | CUGAUGA         | x          | GAA | AAGCUUAU | AUAAGCUUU UAUAUCAC |
|    | 1900 | UGUGAUAU | CUGAUGA         | x          | GAA | AAAGCUUA | UAAGCUUUU AUAUCACA |
|    | 1901 | CUGUGAUA | CUGAUGA         | x          | GAA | AAAAGCUU | AAGCUUUUA UAUCACAG |

|    | 1903 | 3 AUCUGUGA CUGAUGA X GAA AUAAAAGC | GCUUUUAUA UCACAGAU |
|----|------|-----------------------------------|--------------------|
|    | 1905 | ACAUCUGU CUGAUGA X GAA AUAUAAAA   |                    |
|    | 1925 | UAACAUGA CUGAUGA X GAA ACCCAUUU   | AAAUGGGUU UCAUGUUA |
|    | 1926 | UUAACAUG CUGAUGA X GAA AACCCAUU   |                    |
| 5  | 1927 | GUUAACAU CUGAUGA X GAA AAACCCAU   | AUGGGUUUC AUGUUAAC |
|    | 1932 | UCCAAGUU CUGAUGA X GAA ACAUGAAA   | UUUCAUGUU AACUUGGA |
|    | 1933 | UUCCAAGU CUGAUGA X GAA AACAUGAA   | UUCAUGUUA ACUUGGAA |
|    | 1937 | UUUUUUCC CUGAUGA X GAA AGUUAACA   | UGUUAACUU GGAAAAA  |
|    | 1976 | CUGUGCAA CUGAUGA X GAA ACAGUUUC   | GAAACUGUC UUGCACAG |
| 10 | 1978 | AACUGUGC CUGAUGA X GAA AGACAGUU   | AACUGUCUU GCACAGUU |
|    | 1986 | AACUUGUU CUGAUGA X GAA ACUGUGCA   | UGCACAGUU AACAAGUU |
|    | 1987 | GAACUUGU CUGAUGA X GAA AACUGUGC   | GCACAGUUA ACAAGUUC |
|    | 1994 | UGUAUAAG CUGAUGA X GAA ACUUGUUA   | UAACAAGUU CUUAUACA |
|    | 1995 | CUGUAUAA CUGAUGA X GAA AACUUGUU   | AACAAGUUC UUAUACAG |
| 15 | 1997 | STEEDSTID COUNTRY & GAN AGAACUUG  | CAAGUUCUU AUACAGAG |
|    | 1998 | UCUCUGUA CUGAUGA X GAA AAGAACUU   | AAGUUCUUA UACAGAGA |
|    | 2000 | CGUCUCUG CUGAUGA X GAA AUAAGAAC   | GUUCUUAUA CAGAGACG |
|    |      | THE COURS OF A GAA ACGUCUCU       | AGAGACGUU ACUUGGAU |
|    | 2011 | TOTO COURDER & GAA AACGUCUC       | GAGACGUUA CUUGGAUU |
| 20 | 2014 | UAAAAUCC CUGAUGA X GAA AGUAACGU   | ACGUUACUU GGAUUUUA |
|    | 2019 | CGCAGUAA CUGAUGA X GAA AUCCAAGU   | ACUUGGAUU UUACUGCG |
|    | 2020 | CCGCAGUA CUGAUGA X GAA AAUCCAAG   | CUUGGAUUU UACUGCGG |
|    | 2021 | UCCGCAGU CUGAUGA X GAA AAAUCCAA   | UUGGAUUUU ACUGCGGA |
| 25 | 2022 | GUCCGCAG CUGAUGA X GAA AAAAUCCA   | UGGAUUUUA CUGCGGAC |
| 25 |      | CUGUUAUU CUGAUGA X GAA ACUGUCCG   | CGGACAGUU AAUAACAG |
|    |      | AND COMMON & GAN ANCHOUSE         | GGACAGUUA AUAACAGA |
|    |      | UGUUCUGU CUGAUGA X GAA AUUAACUG   | CAGUUAAUA ACAGAACA |
|    | 2054 | UAAUACUG CUGAUGA X GAA AGUGCAUU   | AAUGCACUA CAGUAUUA |
| 20 | 2059 | CUUGCUAA CUGAUGA X GAA ACUGUAGU   | ACUACAGUA UUAGCAAG |
| 30 | 2061 | THE TOTAL STREET A GAR ADACOGUA   | UACAGUAUU AGCAAGCA |
|    | 2062 | THE TOTAL COUNTY OF AND ACORD     | ACAGUAUUA GCAAGCAA |
|    | 2082 | UCCUUAGU CUGAUGA X GAA AUGGCCAU   | AUGGCCAUC ACUAAGGA |
|    | 2086 | GUGCUCCU CUGAUGA X GAA AGUGAUGG   | CCAUCACUA AGGAGCAC |

WO 97/15662

57

PCT/US96/17480

|    | 2096 | GAGUGAUG | CUGAUGA   | . Х | GAA | AGUGCUCC | GGAGCACUC CAUCACUC |
|----|------|----------|-----------|-----|-----|----------|--------------------|
|    | 2100 | UUAAGAGU | CUGAUGA   | . X | GAA | AUGGAGUG | CACUCCAUC ACUCUUAA |
|    | 2104 | AAGAUUAA | CUGAUGA   | . X | GAA | AGUGAUGG | CCAUCACUC UUAAUCUU |
|    | 2106 | GUAAGAUU | CUGAUGA   | X   | GAA | AGAGUGAU | AUCACUCUU AAUCUUAC |
| 5  | 2107 | GGUAAGAU | CUGAUGA   | X   | GAA | AAGAGUGA | UCACUCUUA AUCUUACC |
|    | 2110 | GAUGGUAA | . CUGAUGA | X   | GAA | AUUAAGAG | CUCUUAAUC UUACCAUC |
|    | 2112 | AUGAUGGU | CUGAUGA   | X   | GAA | AGAUUAAG | CUUAAUCUU ACCAUCAU |
|    | 2113 | CAUGAUGG | CUGAUGA   | X   | GAA | AAGAUUAA | UUAAUCUUA CCAUCAUG |
|    | 2118 | ACAUUCAU | CUGAUGA   | X   | GAA | AUGGUAAG | CUUACCAUC AUGAAUGU |
| 10 | 2127 | UGCAGGGA | CUGAUGA   | X   | GAA | ACAUUCAU | AUGAAUGUU UCCCUGCA |
|    | 2128 | UUGCAGGG | CUGAUGA   | X   | GAA | AACAUUCA | UGAAUGUUU CCCUGCAA |
|    | 2129 | CUUGCAGG | CUGAUGA   | X   | GAA | AAACAUUC | GAAUGUUUC CCUGCAAG |
|    | 2140 | GGUGCCUG | CUGAUGA   | X   | GAA | AUCUUGCA | UGCAAGAUU CAGGCACC |
|    | 2141 | AGGUGCCU | CUGAUGA   | X   | GAA | AAUCUUGC | GCAAGAUUC AGGCACCU |
| 15 | 2150 | UGCAGGCA | CUGAUGA   | X   | GAA | AGGUGCCU | AGGCACCUA UGCCUGCA |
|    | 2172 | CCUGUGUA | CUGAUGA   | X   | GAA | ACAUUCCU | AGGAAUGUA UACACAGG |
|    | 2174 | ccccugug | CUGAUGA   | X   | GAA | AUACAUUC | GAAUGUAUA CACAGGGG |
|    | 2190 | UUCUGGAG | CUGAUGA   | x   | GAA | AUUUCUUC | GAAGAAAUC CUCCAGAA |
|    | 2193 | UUCUUCUG | CUGAUGA   | X   | GAA | AGGAUUUC | GAAAUCCUC CAGAAGAA |
| 20 | 2208 | CUGAUUGU | CUGAUGA   | X   | GAA | AUUUCUUU | AAAGAAAUU ACAAUCAG |
|    | 2209 | UCUGAUUG | CUGAUGA   | X   | GAA | AAUUUCUU | AAGAAAUUA CAAUCAGA |
|    | 2214 | UGAUCUCU | CUGAUGA   | X   | GAA | AUUGUAAU | AUUACAAUC AGAGAUCA |
|    | 2221 | UGCUUCCU | CUGAUGA   | X   | GAA | AUCUCUGA | UCAGAGAUC AGGAAGCA |
|    | 2234 | GCAGGAGG | CUGAUGA   | X   | GAA | AUGGUGCU | AGCACCAUA CCUCCUGC |
| 25 | 2238 | UUUCGCAG | CUGAUGA   | X   | GAA | AGGUAUGG | CCAUACCUC CUGCGAAA |
|    | 2250 | UGAUCACU | CUGAUGA   | X   | GAA | AGGUUUCG | CGAAACCUC AGUGAUCA |
|    | 2257 | CACUGUGU | CUGAUGA   | X   | GAA | AUCACUGA | UCAGUGAUC ACACAGUG |
|    | 2271 | GAACUGCU | CUGAUGA   | X   | GAA | AUGGCCAC | GUGGCCAUC AGCAGUUC |
|    | 2278 | AGUGGUGG | CUGAUGA   | X   | GAA | ACUGCUGA | UCAGCAGUU CCACCACU |
| 30 | 2279 | AAGUGGUG | CUGAUGA   | X   | GAA | AACUGCUG | CAGCAGUUC CACCACUU |
|    | 2287 | ACAGUCUA | CUGAUGA   | X   | GAA | AGUGGUGG | CCACCACUU UAGACUGU |
|    | 2288 | GACAGUCU | CUGAUGA   | X   | GAA | AAGUGGUG | CACCACUUU AGACUGUC |
|    | 2289 | UGACAGUC | CUGAUGA   | X   | GAA | AAAGUGGU | ACCACUUUA GACUGUCA |

|    | 2296 | AUUAGCAU   | CUGAUGA |     | GAA | ACAGUCUA | UAGACUGUC AUGCUAAU |
|----|------|------------|---------|-----|-----|----------|--------------------|
|    | 2302 | GACACCAU   | CUGAUGA | . х | GAA | AGCAUGAC | GUCAUGCUA AUGGUGUC |
|    | 2310 | GGCUCGGG   | CUGAUGA | . х | GAA | ACACCAUU | AAUGGUGUC CCCGAGCC |
|    | 2320 | AGUGAUCU   | CUGAUGA | X   | GAA | AGGCUCGG | CCGAGCCUC AGAUCACU |
| 5  | 2325 | AACCAAGU   | CUGAUGA | X   | GAA | AUCUGAGG | CCUCAGAUC ACUUGGUU |
|    | 2329 | UUUAAACC   | CUGAUGA | X   | GAA | AGUGAUCU | AGAUCACUU GGUUUAAA |
|    | 2333 | UGUUUUUA   | CUGAUGA | X   | GAA | ACCAAGUG | CACUUGGUU UAAAAACA |
|    | 2334 | บบเป็นบบบบ | CUGAUGA | X   | GAA | AACCAAGU | ACUUGGUUU AAAAACAA |
|    | 2335 | GUUGUUUU   | CUGAUGA | X   | GAA | AAACCAAG | CUUGGUUUA AAAACAAC |
| 10 | 2352 | UCUUGUUG   | CUGAUGA | X   | GAA | AUUUUGUG | CACAAAAUA CAACAAGA |
|    | 2370 | CCUAAAAU   | CUGAUGA | X   | GAA | AUUCCAGG | CCUGGAAUU AUUUUAGG |
|    | 2371 | UCCUAAAA   | CUGAUGA | X   | GAA | AAUUCCAG | CUGGAAUUA UUUUAGGA |
|    | 2373 | GGUCCUAA   | CUGAUGA | x   | GAA | AUAAUUCC | GGAAUUAUU UUAGGACC |
|    | 2374 | UGGUCCUA   | CUGAUGA | X   | GAA | AAUAAUUC | GAAUUAUUU UAGGACCA |
| 15 | 2375 | CUGGUCCU   | CUGAUGA | X   | GAA | AAAUAAUU | AAUUAUUUU AGGACCAG |
|    | 2376 | CCUGGUCC   | CUGAUGA | X   | GAA | UAAUAAA  | AUUAUUUUA GGACCAGG |
|    | 2399 | UUUCAAUA   | CUGAUGA | X   | GAA | ACAGCGUG | CACGCUGUU UAUUGAAA |
|    | 2400 | CUUUCAAU   | CUGAUGA | X   | GAA | AACAGCGU | ACGCUGUUU AUUGAAAG |
|    | 2401 | UCUUUCAA   | CUGAUGA | X   | GAA | AAACAGCG | CGCUGUUUA UUGAAAGA |
| 20 | 2403 | ACUCUUUC   | CUGAUGA | x   | GAA | AUAAACAG | CUGUUUAUU GAAAGAGU |
|    | 2412 | ncnncnen   | CUGAUGA | X   | GAA | ACUCUUUC | GAAAGAGUC ACAGAAGA |
|    | 2433 | CAGUGAUA   | CUGAUGA | X   | GAA | ACACCUUC | GAAGGUGUC UAUCACUG |
|    | 2435 | UGCAGUGA   | CUGAUGA | X   | GAA | AGACACCU | AGGUGUCUA UCACUGCA |
|    | 2437 | UUUGCAGU   | CUGAUGA | X   | GAA | AUAGACAC | GUGUCUAUC ACUGCAAA |
| 25 | 2465 | UUUCCACA   | CUGAUGA | X   | GAA | AGCCCUUC | GAAGGGCUC UGUGGAAA |
|    | 2476 | GUAUGCUG   | CUGAUGA | X   | GAA | ACUUUCCA | UGGAAAGUU CAGCAUAC |
|    | 2477 | GGUAUGCU   | CUGAUGA | X   | GAA | AACUUUCC | GGAAAGUUC AGCAUACC |
|    | 2483 | CAGUGAGG   | CUGAUGA | X   | GAA | AUGCUGAA | UUCAGCAUA CCUCACUG |
|    | 2487 | UGAACAGU   | CUGAUGA | X   | GAA | AGGUAUGC | GCAUACCUC ACUGUUCA |
| 30 | 2493 | GUUCCUUG   | CUGAUGA | X   | GAA | ACAGUGAG | CUCACUGUU CAAGGAAC |
|    | 2494 | GGUUCCUU   | CUGAUGA | X   | GAA | AACAGUGA | UCACUGUUC AAGGAACC |
|    | 2504 | ACUUGUCC   | CUGAUGA | X   | GAA | AGGUUCCU | AGGAACCUC GGACAAGU |
|    | 2513 | CCAGAUUA   | CUGAUGA | X   | GAA | ACUUGUCC | GGACAAGUC UAAUCUGG |

|    | 2515  | CUCCAGAU CUGAUGA X GAA AGACUUGU | ACAAGUCUA AUCUGGAG |
|----|-------|---------------------------------|--------------------|
|    | 2518  | CAGCUCCA CUGAUGA X GAA AUUAGACU | AGUCUAAUC UGGAGCUG |
|    | 2529  | GUUAGAGU CUGAUGA X GAA AUCAGCUC | GAGCUGAUC ACUCUAAC |
|    | 2533  | GCAUGUUA CUGAUGA X GAA AGUGAUCA | UGAUCACUC UAACAUGC |
| 5  | 2535  | GUGCAUGU CUGAUGA X GAA AGAGUGAU | AUCACUCUA ACAUGCAC |
|    | 2560  | CCAGAAGA CUGAUGA X GAA AGUCGCAG | CUGCGACUC UCUUCUGG |
|    | 2562  | AGCCAGAA CUGAUGA X GAA AGAGUCGC | GCGACUCUC UUCUGGCU |
|    | 2564  | GGAGCCAG CUGAUGA X GAA AGAGAGUC | GACUCUCUU CUGGCUCC |
|    | 2565  | AGGAGCCA CUGAUGA X GAA AAGAGAGU | ACUCUCUUC UGGCUCCU |
| 10 | 2571  | GUUAAUAG CUGAUGA X GAA AGCCAGAA | UUCUGGCUC CUAUUAAC |
|    | 2574  | AGGGUUAA CUGAUGA X GAA AGGAGCCA | UGGCUCCUA UUAACCCU |
|    | .2576 | GGAGGGUU CUGAUGA X GAA AUAGGAGC | GCUCCUAUU AACCCUCC |
|    | 2577  | AGGAGGGU CUGAUGA X GAA AAUAGGAG | CUCCUAUUA ACCCUCCU |
|    | 2583  | CGGAUAAG CUGAUGA X GAA AGGGUUAA | UUAACCCUC CUUAUCCG |
| 15 | 2586  | UUUCGGAU CUGAUGA X GAA AGGAGGGU | ACCCUCCUU AUCCGAAA |
|    | 2587  | UUUUCGGA CUGAUGA X GAA AAGGAGGG | CCCUCCUUA UCCGAAAA |
|    | 2589  | AUUUUUCG CUGAUGA X GAA AUAAGGAG | CUCCUUAUC CGAAAAAU |
|    | 2606  | CAGAAGAA CUGAUGA X GAA ACCUUUUC | GAAAAGGUC UUCUUCUG |
|    | 2608  | UUCAGAAG CUGAUGA X GAA AGACCUUU | AAAGGUCUU CUUCUGAA |
| 20 | 2609  | UUUCAGAA CUGAUGA X GAA AAGACCUU | AAGGUCUUC UUCUGAAA |
|    | 2611  | UAUUUCAG CUGAUGA X GAA AGAAGACC | GGUCUUCUU CUGAAAUA |
|    | 2612  | UUAUUUCA CUGAUGA X GAA AAGAAGAC | GUCUUCUUC UGAAAUAA |
|    | 2619  | UCAGUCUU CUGAUGA X GAA AUUUCAGA | UCUGAAAUA AAGACUGA |
|    | 2630  | UUGAUAGG CUGAUGA X GAA AGUCAGUC |                    |
| 25 |       | AUAAUUGA CUGAUGA X GAA AGGUAGUC |                    |
|    |       | UUAUAAUU CUGAUGA X GAA AUAGGUAG |                    |
|    |       | UCCAUUAU CUGAUGA X GAA AUUGAUAG | CUAUCAAUU AUAAUGGA |
|    | 2641  | GUCCAUUA CUGAUGA X GAA AAUUGAUA | UAUCAAUUA UAAUGGAC |
|    | 2643  | GGGUCCAU CUGAUGA X GAA AUAAUUGA | UCAAUUAUA AUGGACCC |
| 30 | 2661  | UCCAAAGG CUGAUGA X GAA ACUUCAUC | GAUGAAGUU CCUUUGGA |
|    | 2662  | AUCCAAAG CUGAUGA X GAA AACUUCAU | AUGAAGUUC CUUUGGAU |
|    | 2665  | CUCAUCCA CUGAUGA X GAA AGGAACUU | AAGUUCCUU UGGAUGAG |
|    | 2666  | GCUCAUCC CUGAUGA X GAA AAGGAACU | AGUUCCUUU GGAUGAGC |

|    | 2688 | UCAUAAGG CUGAUGA X GAA AGCCGCUC | GAGCGGCUC CCUUAUGA |
|----|------|---------------------------------|--------------------|
|    | 2692 | GGCAUCAU CUGAUGA X GAA AGGGAGCC | GGCUCCCUU AUGAUGCC |
|    | 2693 | UGGCAUCA CUGAUGA X GAA AAGGGAGC | GCUCCCUUA UGAUGCCA |
|    | 2714 | CCCGGGCA CUGAUGA X GAA ACUCCCAC | GUGGGAGUU UGCCCGGG |
| 5  | 2715 | UCCCGGGC CUGAUGA X GAA AACUCCCA | UGGGAGUUU GCCCGGGA |
|    | 2730 | CCCAGUUU CUGAUGA X GAA AGUCUCUC | GAGAGACUU AAACUGGG |
|    | 2731 | GCCCAGUU CUGAUGA X GAA AAGUCUCU | AGAGACUUA AACUGGGC |
|    | 2744 | UUCCAAGU CUGAUGA X GAA AUUUGCCC | GGGCAAAUC ACUUGGAA |
|    | 2748 | CCUCUUCC CUGAUGA X GAA AGUGAUUU | AAAUCACUU GGAAGAGG |
| 10 | 2761 | UUUUCCAA CUGAUGA X GAA AGCCCCUC | GAGGGGCUU UUGGAAAA |
|    | 2762 | CUUUUCCA CUGAUGA X GAA AAGCCCCU | AGGGGCUUU UGGAAAAG |
|    | 2763 | ACUUUUCC CUGAUGA X GAA AAAGCCCC | GGGGCUUUU GGAAAAGU |
|    | 2775 | GAUGCUUG CUGAUGA X GAA ACCACUUU | AAAGUGGUU CAAGCAUC |
|    | 2776 | UGAUGCUU CUGAUGA X GAA AACCACUU | AAGUGGUUC AAGCAUCA |
| 15 | 2783 | CAAAUGCU CUGAUGA X GAA AUGCUUGA | UCAAGCAUC AGCAUUUG |
|    | 2789 | UAAUGCCA CUGAUGA X GAA AUGCUGAU | AUCAGCAUD UGGCAUUA |
|    | 2790 | UUAAUGCC CUGAUGA X GAA AAUGCUGA | UCAGCAUUU GGCAUUAA |
|    | 2796 | GAUUUCUU CUGAUGA X GAA AUGCCAAA | UUUGGCAUU AAGAAAUC |
|    | 2797 | UGAUUUCU CUGAUGA X GAA AAUGCCAA | UUGGCAUUA AGAAAUCA |
| 20 | 2804 | ACGUAGGU CUGAUGA X GAA AUUUCUUA | UAAGAAAUC ACCUACGU |
|    | 2809 | CCGGCACG CUGAUGA X GAA AGGUGAUU | AAUCACCUA CGUGCCGG |
|    | 2864 | GAGCUUUG CUGAUGA X GAA ACUCGCUG | CAGCGAGUA CAAAGCUC |
|    | 2872 | AGUCAUCA CUGAUGA X GAA AGCUUUGU | ACAAAGCUC UGAUGACU |
|    | 2886 | AAGAUUUU CUGAUGA X GAA AGCUCAGU | ACUGAGCUA AAAAUCUU |
| 25 | 2892 | UGGGUCAA CUGAUGA X GAA AUUUUUAG | CUAAAAAUC UUGACCCA |
|    | 2894 | UGUGGGUC CUGAUGA X GAA AGAUUUUU | AAAAAUCUU GACCCACA |
|    | 2904 | UGGUGGCC CUGAUGA X GAA AUGUGGGU | ACCCACAUU GGCCACCA |
|    | 2914 | CACGUUCA CUGAUGA X GAA AUGGUGGC | GCCACCAUC UGAACGUG |
|    | 2925 | AGCAGGUU CUGAUGA X GAA ACCACGUU | AACGUGGUU AACCUGCU |
| 30 | 2926 | CAGCAGGU CUGAUGA X GAA AACCACGU | ACGUGGUUA ACCUGCUG |
|    | 2962 | CACCAUCA CUGAUGA X GAA AGGCCCUC | GAGGGCCUC UGAUGGUG |
|    | 2973 | UAUUCAAC CUGAUGA X GAA AUCACCAU | AUGGUGAUU GUUGAAUA |
|    | 2976 | CAGUAUUC CUGAUGA X GAA ACAAUCAC | GUGAUUGUU GAAUACUG |

PCT/US96/17480 WO 97/15662

|    | 2981 | AUUUGCAG | CUGAUGA | X          | GAA | AUUCAACA | UGUUGAAUA CUGCAAAU |
|----|------|----------|---------|------------|-----|----------|--------------------|
|    | 2990 | GAUUUCCA | CUGAUGA | X          | GAA | AUUUGCAG | CUGCAAAUA UGGAAAUC |
|    | 2998 | GUUGGAGA | CUGAUGA | X          | GAA | AUUUCCAU | AUGGAAAUC UCUCCAAC |
|    | 3000 | UAGUUGGA | CUGAUGA | . x        | GAA | AGAUUUCC | GGAAAUCUC UCCAACUA |
| 5  | 3002 | GGUAGUUG | CUGAUGA | . <b>x</b> | GAA | AGAGAUUU | AAAUCUCUC CAACUACC |
|    | 3008 | UCUUGAGG | CUGAUGA | X          | GAA | AGUUGGAG | CUCCAACUA CCUCAAGA |
|    | 3012 | UUGCUCUU | CUGAUGA | X          | GAA | AGGUAGUU | AACUACCUC AAGAGCAA |
|    | 3029 | GAAAAAAU | CUGAUGA | X          | GAA | AGUCACGU | ACGUGACUU AUUUUUUC |
|    | 3030 | AGAAAAA  | CUGAUGA | X          | GAA | AAGUCACG | CGUGACUUA UUUUUUCU |
| 10 | 3032 | UGAGAAAA | CUGAUGA | X          | GAA | AUAAGUCA | UGACUUAUU UUUUCUCA |
|    | 3033 | UUGAGAAA | CUGAUGA | X          | GAA | AAUAAGUC | GACUUAUUU UUUCUCAA |
|    | 3034 | GUUGAGAA | CUGAUGA | X          | GAA | AAAUAAGU | ACUUAUUUU UUCUCAAC |
|    | 3035 | UGUUGAGA | CUGAUGA | X          | GAA | AAAAUAAG | CUUAUUUUU UCUCAACA |
|    | 3036 | UUGUUGAG | CUGAUGA | X          | GAA | AAAAAUAA | UUAUUUUUU CUCAACAA |
| 15 | 3037 | CUUGUUGA | CUGAUGA | X          | GAA | AAAAAAUA | UAUUUUUC UCAACAAG  |
|    | 3039 | UCCUUGUU | CUGAUGA | x          | GAA | AGAAAAA  | UUUUUUCUC AACAAGGA |
|    | 3057 | UCCAUGUG | CUGAUGA | X          | GAA | AGUGCUGC | GCAGCACUA CACAUGGA |
|    | 3070 | υυςυυυςυ | CUGAUGA | X          | GAA | AGGCUCCA | UGGAGCCUA AGAAAGAA |
|    | 3120 | ACGCUAUC | CUGAUGA | X          | GAA | AGUCUUGG | CCAAGACUA GAUAGCGU |
| 20 | 3124 | GGUGACGC | CUGAUGA | X          | GAA | AUCUAGUC | GACUAGAUA GCGUCACC |
|    | 3129 | CUGCUGGU | CUGAUGA | X          | GAA | ACGCUAUC | GAUAGCGUC ACCAGCAG |
|    | 3146 | AGCUCGCA | CUGAUGA | X          | GAA | AGCUUUCG | CGAAAGCUU UGCGAGCU |
|    | 3147 | GAGCUCGC | CUGAUGA | X          | GAA | AAGCUUUC | GAAAGCUUU GCGAGCUC |
|    | 3155 | GAAAGCCG | CUGAUGA | X          | GAA | AGCUCGCA | UGCGAGCUC CGGCUUUC |
| 25 | 3161 | CUUCCUGA | CUGAUGA | x          | GAA | AGCCGGAG | CUCCGGCUU UCAGGAAG |
|    | 3162 | UCUUCCUG | CUGAUGA | X          | GAA | AAGCCGGA | UCCGGCUUU CAGGAAGA |
|    | 3163 | AUCUUCCU | CUGAUGA | x          | GAA | AAAGCCGG | CCGGCUUUC AGGAAGAU |
|    | 3172 | CAGACUUU | CUGAUGA | X          | GAA | AUCUUCCU | AGGAAGAUA AAAGUCUG |
|    | 3178 | AUCACUCA | CUGAUGA | X          | GAA | ACUUUUAU | AUAAAAGUC UGAGUGAU |
| 30 | 3189 | חכחחככחכ | CUGAUGA | X          | GAA | ACAUCACU | AGUGAUGUU GAGGAAGA |
|    | 3205 | ACCGUCAG | CUGAUGA | X          | GAA | AUCCUCCU | AGGAGGAUU CUGACGGU |
|    | 3206 | AACCGUCA | CUGAUGA | X          | GAA | AAUCCUCC | GGAGGAUUC UGACGGUU |
|    | 3214 | CUUGUAGA | CUGAUGA | X          | GAA | ACCGUCAG | CUGACGGUU UCUACAAG |

|    | 3215 | CCUUGUAG | CUGAUGA | X | GAA | AACCGUCA | UGACGGUUU | CUACAAGG |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 3216 | UCCUUGUA | CUGAUGA | x | GAA | AAACCGUC | GACGGUUUC | UACAAGGA |
|    | 3218 | GCUCCUUG | CUGAUGA | X | GAA | AGAAACCG | CGGUUUCUA | CAAGGAGC |
|    | 3231 | UCCAUAGU | CUGAUGA | X | GAA | AUGGGCUC | GAGCCCAUC | ACUAUGGA |
| 5  | 3235 | AUCUUCCA | CUGAUGA | X | GAA | AGUGAUGG | CCAUCACUA | UGGAAGAU |
|    | 3244 | AGAAAUCA | CUGAUGA | x | GAA | AUCUUCCA | UGGAAGAUC | UGAUUUCU |
|    | 3249 | CUGUAAGA | CUGAUGA | x | GAA | AUCAGAUC | GAUCUGAUU | UCUUACAG |
|    | 3250 | ACUGUAAG | CUGAUGA | x | GAA | AAUCAGAU | AUCUGAUUU | CUUACAGU |
|    | 3251 | AACUGUAA | CUGAUGA | x | GAA | AAAUCAGA | UCUGAUUUC | UUACAGUU |
| 10 | 3253 | AAAACUGU | CUGAUGA | x | GAA | AGAAAUCA | UGAUUUCUU | ACAGUUUU |
|    | 3254 | GAAAACUG | CUGAUGA | x | GAA | AAGAAAUC | GAUUUCUUA | CAGUUUUC |
|    | 3259 | CACUUGAA | CUGAUGA | x | GAA | ACUGUAAG | CUUACAGUU | UUCAAGUG |
|    | 3260 | CCACUUGA | CUGAUGA | X | GAA | AACUGUAA | UUACAGUUU | UCAAGUGG |
|    | 3261 | GCCACUUG | CUGAUGA | x | GAA | AAACUGUA | UACAGUUUU | CAAGUGGC |
| 15 | 3262 | GGCCACUU | CUGAUGA | x | GAA | AAAACUGU | ACAGUUUUC | AAGUGGCC |
|    | 3284 | AAGACAGG | CUGAUGA | x | GAA | ACUCCAUG | CAUGGAGUU | ccugucuu |
|    | 3285 | GAAGACAG | CUGAUGA | x | GAA | AACUCCAU | AUGGAGUUC | CUGUCUUC |
|    | 3290 | UUCUGGAA | CUGAUGA | X | GAA | ACAGGAAC | GUUCCUGUC | UUCCAGAA |
|    | 3292 | CUUUCUGG | CUGAUGA | x | GAA | AGACAGGA | UCCUGUCUU | CCAGAAAG |
| 20 | 3293 | ACUUUCUG | CUGAUGA | x | GAA | AAGACAGG | CCUGUCUUC | CAGAAAGU |
|    | 3306 | UCCCGAUG | CUGAUGA | x | GAA | AUGCACUU | AAGUGCAUU | CAUCGGGA |
|    | 3307 | GUCCCGAU | CUGAUGA | x | GAA | AAUGCACU | AGUGCAUUC | AUCGGGAC |
|    | 3310 | CAGGUCCC | CUGAUGA | x | GAA | AUGAAUGC | GCAUUCAUC | GGGACCUG |
|    | 3333 | GAUAAAAG | CUGAUGA | x | GAA | AUGUUUCU | AGAAACAUU | CUUUUAUC |
| 25 | 3334 | AGAUAAAA | CUGAUGA | x | GAA | AAUGUUUC | GAAACAUUC | UUUUAUCU |
|    | 3336 | UCAGAUAA | CUGAUGA | x | GAA | AGAAUGUU | AACAUUCUU | UUAUCUGA |
|    | 3337 | CUCAGAUA | CUGAUGA | X | GAA | AAGAAUGU | ACAUUCUUU | UAUCUGAG |
|    | 3338 | UCUCAGAU | CUGAUGA | X | GAA | AAAGAAUG | CAUUCUUUU | AUCUGAGA |
|    | 3339 | UUCUCAGA | CUGAUGA | x | GAA | AAAAGAAU | AUUCUUUUA | UCUGAGAA |
| 30 | 3341 | UGUUCUCA | CUGAUGA | x | GAA | AUAAAAGA | UCUUUUAUC | UGAGAACA |
|    | 3363 | AAAUCACA | CUGAUGA | X | GAA | AUCUUCAC | GUGAAGAUU | UGUGAUUU |
|    | 3364 | AAAAUCAC | CUGAUGA | x | GAA | AAUCUUCA | UGAAGAUUU | GUGAUUUU |
|    | 3370 | AAGGCCAA | CUGAUGA | x | GAA | AUCACAAA | UUUGUGAUU | UUGGCCUU |

PCT/US96/17480

WO 97/15662

|    | 3371 | CAAGGCCA | CUGAUGA | . X | GAA | AAUCACAA | UUGUGAUUU UGGC  | CUUG:        |
|----|------|----------|---------|-----|-----|----------|-----------------|--------------|
|    | 3372 | GCAAGGCC | CUGAUGA | X   | GAA | AAAUCACA | UGUGAUUUU GGCC  | TUGC         |
|    | 3378 | UCCCGGGC | CUGAUGA | X   | GAA | AGGCCAAA | uuuggccuu gccc  | GGGA         |
|    | 3388 | CUUAUAAA | CUGAUGA | X   | GAA | AUCCCGGG | CCCGGGAUA UUUA  | UAAG         |
| 5  | 3390 | UUCUUAUA | CUGAUGA | X   | GAA | AUAUCCCG | CGGGAUAUU UAUA  | AGAA         |
|    | 3391 | GUUCUUAU | CUGAUGA | X   | GAA | AAUAUCCC | GGGAUAUUU AUAA  | GAAC         |
|    | 3392 | GGUUCUUA | CUGAUGA | X   | GAA | AAAUAUCC | GGAUAUUUA UAAG  | AACC         |
| ٠  | 3394 | GGGGUUCU | CUGAUGA | X   | GAA | AUAAAUAU | AUAUUUAUA AGAA  | CCCC         |
|    | 3406 | UCUCACAU | CUGAUGA | X   | GAA | AUCGGGGU | ACCCCGAUU AUGU  | GAGA         |
| 10 | 3407 | UUCUCACA | CUGAUGA | X   | GAA | AAUCGGGG | CCCCGAUUA UGUG  | AGAA         |
|    | 3424 | AAGUCGAG | CUGAUGA | X   | GAA | AUCUCCUU | AAGGAGAUA CUCG  | ACUU         |
|    | 3427 | AGGAAGUC | CUGAUGA | x   | GAA | AGUAUCUC | GAGAUACUC GACU  | UCCU         |
|    | 3432 | UUCAGAGG | CUGAUGA | X   | GAA | AGUCGAGU | ACUCGACUU CCUCT | JGAA         |
|    | 3433 | UUUCAGAG | CUGAUGA | X   | GAA | AAGUCGAG | CUCGACUUC CUCUC | SAAA         |
| 15 | 3436 | CCAUUUCA | CUGAUGA | X   | GAA | AGGAAGUC | GACUUCCUC UGAAI | <b>\UGG</b>  |
|    | 3451 | AGAUUCGG | CUGAUGA | X   | GAA | AGCCAUCC | GGAUGGCUC CCGAI | <b>YUC</b> U |
|    | 3458 | CAAAGAUA | CUGAUGA | X   | GAA | AUUCGGGA | UCCCGAAUC UAUCU | JUUG         |
|    | 3460 | GUCAAAGA | CUGAUGA | X   | GAA | AGAUUCGG | CCGAAUCUA UCUUL | JGAC         |
|    | 3462 | UUGUCAAA | CUGAUGA | X   | GAA | AUAGAUUC | GAAUCUAUC UUUGA | <b>ICAA</b>  |
| 20 | 3464 | UUUUGUCA | CUGAUGA | X   | GAA | AGAUAGAU | AUCUAUCUU UGACA | AAA          |
|    | 3465 | AUUUUGUC | CUGAUGA | X   | GAA | AAGAUAGA | UCUAUCUUU GACAA | UAAU         |
|    | 3474 | GUGCUGUA | CUGAUGA | X   | GAA | AUUUUGUC | GACAAAAUC UACAG | CAC          |
|    | 3476 | UGGUGCUG | CUGAUGA | X   | GAA | AGAUUUUG | CAAAAUCUA CAGCA | LCCA         |
|    | 3500 | CUCCGUAA | CUGAUGA | X   | GAA | ACCACACG | CGUGUGGUC UUACG | GAG          |
| 25 | 3502 | UACUCCGU | CUGAUGA | X   | GAA | AGACCACA | UGUGGUCUU ACGGA | LGUA         |
|    | 3503 | AUACUCCG | CUGAUGA | X   | GAA | AAGACCAC | GUGGUCUUA CGGAG | UAU          |
|    | 3510 | CACAGCAA | CUGAUGA | X   | GAA | ACUCCGUA | UACGGAGUA UUGCU | IGUG         |
|    | 3512 | CCCACAGC | CUGAUGA | X   | GAA | AUACUCCG | CGGAGUAUU GCUGU | IGGG         |
|    | 3525 | AAGGAGAA | CUGAUGA | X   | GAA | AUUUCCCA | UGGGAAAUC UUCUC | :כטט         |
| 30 | 3527 | CUAAGGAG | CUGAUGA | X   | GAA | AGAUUUCC | GGAAAUCUU CUCCU | JUAG         |
|    | 3528 | CCUAAGGA | CUGAUGA | X   | GAA | AAGAUUUC | GAAAUCUUC UCCUU | IAGG         |
|    | 3530 | CACCUAAG | CUGAUGA | X   | GAA | AGAAGAUU | AAUCUUCUC CUUAG | GUG          |
|    | 3533 | ACCCACCU | CUGAUGA | X   | GAA | AGGAGAAG | CUUCUCCUU AGGUG | :GGU         |
|    |      |          |         |     |     |          |                 |              |

|    | 3534 | GACCCACC | CUGAUGA | X   | GAA | AAGGAGAA   | ບບດດດດດາ  | A GGUGGGUC |
|----|------|----------|---------|-----|-----|------------|-----------|------------|
|    | 3542 | GGUAUGGA | CUGAUGA | X   | GAA | ACCCACCU   | AGGUGGGU  | UCCAUACO   |
|    | 3544 | UGGGUAUG | CUGAUGA | X   | GAA | AGACCCAC   | GUGGGUCUC | CAUACCCA   |
|    | 3548 | CUCCUGGG | CUGAUGA | . x | GAA | AUGGAGAC   | GUCUCCAUA | CCCAGGAG   |
| 5  | 3558 | UCCAUUUG | CUGAUGA | X   | GAA | ACUCCUGG   | CCAGGAGUA | CAAAUGGA   |
|    | 3575 | GACUGCAA | CUGAUGA | X   | GAA | AGUCCUCA   | UGAGGACUU | UUGCAGUC   |
|    | 3576 | CGACUGCA | CUGAUGA | X   | GAA | AAGUCCUC   | GAGGACUUU | UGCAGUCG   |
|    | 3577 | GCGACUGC | CUGAUGA | x   | GAA | AAAGUCCU   | AGGACUUUU | GCAGUCGC   |
|    | 3583 | CCUCAGGC | CUGAUGA | X   | GAA | ACUGCAAA   | UUUGCAGUC | GCCUGAGG   |
| 10 | 3613 | GUACUCAG | CUGAUGA | X   | GAA | AGCUCUCA   | UGAGAGCUC | CUGAGUAC   |
|    | 3620 | GAGUAGAG | CUGAUGA | X   | GAA | ACUCAGGA   | UCCUGAGUA | CUCUACUC   |
|    | 3623 | CAGGAGUA | CUGAUGA | X   | GAA | AGUACUCA   | UGAGUACUC | UACUCCUG   |
|    | 3625 | UUCAGGAG | CUGAUGA | X   | GAA | AGAGUACU   | AGUACUCUA | CUCCUGAA   |
|    | 3628 | GAUUUCAG | CUGAUGA | X   | GAA | AGUAGAGU   | ACUCUACUC | CUGAAAUC   |
| 15 | 3636 | AUCUGAUA | CUGAUGA | X   | GAA | AUUUCAGG   | CCUGAAAUC | UAUCAGAU   |
|    | 3638 | UGAUCUGA | CUGAUGA | X   | GAA | AGAUUUCA   | UGAAAUCUA | UCAGAUCA   |
|    | 3640 | CAUGAUCU | CUGAUGA | X   | GAA | AUAGAUUU   | AAAUCUAUC | AGAUCAUG   |
|    | 3645 | UCCAGCAU | CUGAUGA | X   | GAA | AUCUGAUA   | UAUCAGAUC | AUGCUGGA   |
|    | 3689 | GUUCUGCA | CUGAUGA | X   | GAA | AUCUUGGC   | GCCAAGAUU | UGCAGAAC   |
| 20 | 3690 | AGUUCUGC | CUGAUGA | X   | GAA | AAUCUUGG   | CCAAGAUUU | GCAGAACU   |
|    | 3699 | UUUUCCAC | CUGAUGA | x   | GAA | AGUUCUGC   | GCAGAACUU | GUGGAAAA   |
|    | 3711 | AAAUCACC | CUGAUGA | X   | GAA | AGUUUUUC   | GAAAAACUA | GGUGAUUU   |
|    | 3718 | UUGAAGCA | CUGAUGA | X   | GAA | AUCACCUA   | UAGGUGAUU | UGCUUCAA   |
|    | 3719 | CUUGAAGC | CUGAUGA | x   | GAA | AAUCACCU   | AGGUGAUUU | GCUUCAAG   |
| 25 | 3723 | UUUGCUUG | CUGAUGA | X   | GAA | AGCAAAUC   | GAUUUGCUU | CAAGCAAA   |
|    | 3724 | AUUUGCUU | CUGAUGA | X   | GAA | AAGCAAAU   | AUUUGCUUC | AAGCAAAU   |
|    | 3735 | UCCUGUUG | CUGAUGA | x   | GAA | ACAUUUGC   | GCAAAUGUA | CAACAGGA   |
|    | 3748 | GUAGUCUU | CUGAUGA | X   | GAA | ACCAUCCU   | AGGAUGGUA | AAGACUAC   |
|    | 3755 | UUGGGAUG | CUGAUGA | x   | GAA | AGUCUUUA   | UAAAGACUA | CAUCCCAA   |
| 30 | 3759 | UUGAUUGG | CUGAUGA | X   | GAA | AUGUAGUC ( | GACUACAUC | CCAAUCAA   |
|    | 3765 | AUGGCAUU | CUGAUGA | X   | GAA | AUUGGGAU   | AUCCCAAUC | AAUGCCAU   |
|    | 3774 | CCUGUCAG | CUGAUGA | X   | GAA | AUGGCAUU   | AAUGCCAUA | CUGACAGG   |
|    | 3787 | AAACCCAC | CUGAUGA | x   | GAA | AUUUCCUG   | CAGGAAAUA | GUGGGUUU   |
|    |      |          |         |     |     |            |           |            |

|    | 3794 | AGUAUGUA | CUGAUGA | x | GAA | ACCCACUA | UAGUGGGUU | UACAUACU |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 3795 | GAGUAUGU | CUGAUGA | x | GAA | AACCCACU | AGUGGGUUU | ACAUACUC |
|    | 3796 | UGAGUAUG | CUGAUGA | x | GAA | AAACCCAC | GUGGGUUUA | CAUACUCA |
|    | 3800 | GAGUUGAG | CUGAUGA | x | GAA | AUGUAAAC | GUUUACAUA | CUCAACUC |
| 5  | 3803 | CAGGAGUU | CUGAUGA | x | GAA | AGUAUGUA | UACAUACUC | AACUCCUG |
|    | 3808 | GAAGGCAG | CUGAUGA | X | GAA | AGUUGAGU | ACUCAACUC | CUGCCUUC |
|    | 3815 | CCUCAGAG | CUGAUGA | X | GAA | AGGCAGGA | uccugccuu | CUCUGAGG |
|    | 3816 | UCCUCAGA | CUGAUGA | x | GAA | AAGGCAGG | CCUGCCUUC | UCUGAGGA |
|    | 3818 | AGUCCUCA | CUGAUGA | X | GAA | AGAAGGCA | UGCCUUCUC | UGAGGACU |
| 10 | 3827 | CCUUGAAG | CUGAUGA | x | GAA | AGUCCUCA | UGAGGACUU | CUUCAAGG |
|    | 3828 | UCCUUGAA | CUGAUGA | x | GAA | AAGUCCUC | GAGGACUUC | UUCAAGGA |
|    | 3830 | UUUCCUUG | CUGAUGA | x | GAA | AGAAGUCC | GGACUUCUU | CAAGGAAA |
|    | 3831 | CUUUCCUU | CUGAUGA | x | GAA | AAGAAGUC | GACUUCUUC | AAGGAAAG |
|    | 3841 | AGCUGAAA | CUGAUGA | x | GAA | ACUUUCCU | AGGAAAGUA | UUUCAGCU |
| 15 | 3843 | GGAGCUGA | CUGAUGA | x | GAA | AUACUUUC | GAAAGUAUU | UCAGCUCC |
|    | 3844 | CGGAGCUG | CUGAUGA | X | GAA | AAUACUUU | AAAGUAUUU | CAGCUCCG |
|    | 3845 | UCGGAGCU | CUGAUGA | x | GAA | AAAUACUU | AAGUAUUUC | AGCUCCGA |
|    | 3850 | AAACUUCG | CUGAUGA | x | GAA | AGCUGAAA | UUUCAGCUC | CGAAGUUU |
|    | 3857 | CUGAAUUA | CUGAUGA | x | GAA | ACUUCGGA | UCCGAAGUU | UAAUUCAG |
| 20 | 3858 | CCUGAAUU | CUGAUGA | X | GAA | AACUUCGG | CCGAAGUUU | AAUUCAGG |
|    | 3859 | UCCUGAAU | CUGAUGA | X | GAA | AAACUUCG | CGAAGUUUA | AUUCAGGA |
|    | 3862 | GCUUCCUG | CUGAUGA | x | GAA | AUUAAACU | AGUUUAAUU | CAGGAAGC |
|    | 3863 | AGCUUCCU | CUGAUGA | x | GAA | AAUUAAAC | GUUUAAUUC | AGGAAGCU |
|    | 3872 | CAUCAUCA | CUGAUGA | x | GAA | AGCUUCCU | AGGAAGCUC | UGAUGAUG |
| 25 | 3882 | ACAUAUCU | CUGAUGA | x | GAA | ACAUCAUC | GAUGAUGUC | agauaugu |
|    | 3887 | CAUUUACA | CUGAUGA | x | GAA | AUCUGACA | UGUCAGAUA | UGUAAAUG |
|    | 3891 | AAAGCAUU | CUGAUGA | x | GAA | ACAUAUCU | AGAUAUGUA | AAUGCUUU |
|    | 3898 | GAACUUGA | CUGAUGA | x | GAA | AGCAUUUA | UAAAUGCUU | UCAAGUUC |
|    | 3899 | UGAACUUG | CUGAUGA | x | GAA | AAGCAUUU | AAAUGCUUU | CAAGUUCA |
| 30 | 3900 | AUGAACUU | CUGAUGA | X | GAA | AAAGCAUU | AAUGCUUUC | AAGUUCAU |
|    | 3905 | GGCUCAUG | CUGAUGA | X | GAA | ACUUGAAA | UUUCAAGUU | CAUGAGCC |
|    | 3906 | AGGCUCAU | CUGAUGA | X | GAA | AACUUGAA | UUCAAGUUC | AUGAGCCU |
|    | 3924 | AAGGUUUU | CUGAUGA | X | GAA | AUUCUUUC | GAAAGAAUC | AAAACCUU |
|    |      |          |         |   |     |          |           |          |

|    | 3932 | GUUCUUC  | A CUGAUGI | A 2        | ( GA) | A AGGUUUUG | CAAAACCUU UGAAGAAC |
|----|------|----------|-----------|------------|-------|------------|--------------------|
|    | 3933 | AGUUCUU  | CUGAUG    | A 2        | ( GA  | A AAGGUUUU | AAAACCUUU GAAGAACU |
|    | 3942 | UUCGGUA  | A CUGAUG  | <b>A</b> 3 | GA/   | A AGUUCUUC | GAAGAACUU UUACCGAA |
|    | 3943 | AUUCGGUA | A CUGAUGA | <b>.</b> , | GAZ   | A AAGUUCUU | AAGAACUUU UACCGAAU |
| 5  | 3944 | CAUUCGGU | J CUGAUGA | <b>A</b> 3 | GAZ   | AAAGUUCU   | AGAACUUUU ACCGAAUG |
|    | 3945 | GCAUUCGG | CUGAUGA   | K          | GAZ   | AAAAGUUC   | GAACUUUUA CCGAAUGC |
|    | 3959 | CAAACAUG | CUGAUGA   | X          | GAA   | AGGUGGCA   | UGCCACCUC CAUGUUUG |
|    | 3965 | AGUCAUCA | CUGAUGA   | X          | GAA   | ACAUGGAG   | CUCCAUGUU UGAUGACU |
|    | 3966 | UAGUCAUC | CUGAUGA   | X          | GAA   | AACAUGGA   | UCCAUGUUU GAUGACUA |
| 10 | 3974 | CGCCCUGG | CUGAUGA   | ×          | GAA   | AGUCAUCA   | UGAUGACUA CCAGGGCG |
|    | 3994 | GGCCAACA | CUGAUGA   | X          | GAA   | AGUGCUGC   | GCAGCACUC UGUUGGCC |
|    | 3998 | GAGAGGCC | CUGAUGA   | X          | GAA   | ACAGAGUG   | CACUCUGUU GGCCUCUC |
|    | 4004 | GCAUGGGA | CUGAUGA   | X          | GAA   | AGGCCAAC   | GUUGGCCUC UCCCAUGC |
|    | 4006 | CAGCAUGG | CUGAUGA   | X          | GAA   | AGAGGCCA   | UGGCCUCUC CCAUGCUG |
| 15 | 4022 | UCCAGGUG | CUGAUGA   | x          | GAA   | AGCGCUUC   | GAAGCGCUU CACCUGGA |
|    | 4023 | GUCCAGGU | CUGAUGA   | x          | 37.A  | AAGCGCUU   | AAGCGCUUC ACCUGGAC |
|    | 4052 | UCUUGAGC | CUGAUGA   | x          | GAA   | AGGCCUUG   | CAAGGCCUC GCUCAAGA |
|    | 4056 | UCAAUCUU | CUGAUGA   | x          | GAA   | AGCGAGGC   | GCCUCGCUC AAGAUUGA |
|    | 4062 | CUCAAGUC | CUGAUGA   | x          | GAA   | AUCUUGAG   | CUCAAGAUU GACUUGAG |
| 20 | 4067 | UUACUCUC | CUGAUGA   | x          | GAA   | AGUCAAUC   | GAUUGACUU GAGAGUAA |
|    | 4074 | UUACUGGU | CUGAUGA   | x          | GAA   | ACUCUCAA   | UUGAGAGUA ACCAGUAA |
|    | 4081 | CUUACUUU | CUGAUGA   | x          | GAA   | ACUGGUUA   | UAACCAGUA AAAGUAAG |
|    | 4087 | CGACUCCU | CUGAUGA   | x          | GAA   | ACUUUUAC   | GUAAAAGUA AGGAGUCG |
|    | 4094 | ACAGCCCC | CUGAUGA   | x          | GAA   | ACUCCUUA   | UAAGGAGUC GGGGCUGU |
| 25 | 4103 | UGACAUCA | CUGAUGA   | x          | GAA   | ACAGCCCC   | GGGGCUGUC UGAUGUCA |
|    | 4110 | GGCCUGCU | CUGAUGA   | x          | GAA   | ACAUCAGA   | UCUGAUGUC AGCAGGCC |
|    | 4123 | AUGGCAGA | CUGAUGA   | x          | GAA   | ACUGGGCC   | GGCCCAGUU UCUGCCAU |
|    | 4124 | AAUGGCAG | CUGAUGA   | x          | GAA   | AACUGGGC   | GCCCAGUUU CUGCCAUU |
|    | 4125 | GAAUGGCA | CUGAUGA   | x          | GAA   | AAACUGGG   | CCCAGUUUC UGCCAUUC |
| 30 | 4132 | ACAGCUGG | CUGAUGA   | X          | GAA   | AUGGCAGA   | UCUGCCAUU CCAGCUGU |
|    | 4133 | CACAGCUG | CUGAUGA   | x          | GAA   | AAUGGCAG   | CUGCCAUUC CAGCUGUG |
|    | 4149 | CCUUCGCU | CUGAUGA   | x          | GAA   | ACGUGCCC   | GGGCACGUC AGCGAAGG |
|    | 4169 | CGUAGGUG | CUGAUGA   | x          | GAA   | ACCUGCGC   | GCGCAGGUU CACCUACG |

PCT/US96/17480 WO 97/15662

|    | 4170 | UCGUAGGU | CUGAUGA | . x | GAA | AACCUGCG         | CGCAGGUUC | ACCUACGA |
|----|------|----------|---------|-----|-----|------------------|-----------|----------|
|    | 4175 | CGUGGUCG | CUGAUGA | x   | GAA | AGGUGAAC         | GUUCACCUA | CGACCACG |
|    | 4203 | CAGCACGC | CUGAUGA | X   | GAA | AUUUUCCU         | AGGAAAAUC | GCGUGCUG |
|    | 4214 | GGGGCGGG | CUGAUGA | x   | GAA | AGCAGCAC         | GUGCUGCUC | ccccccc  |
| 5  | 4229 | CCGAGUUG | CUGAUGA | X   | GAA | AGUCUGGG         | CCCAGACUA | CAACUCGG |
|    | 4235 | GGACCACC | CUGAUGA | X   | GAA | AGUUGUAG         | CUACAACUC | GGUGGUCC |
|    | 4242 | GAGUACAG | CUGAUGA | X   | GAA | ACCACCGA         | UCGGUGGUC | CUGUACUC |
|    | 4247 | GGGUGGAG | CUGAUGA | X   | GAA | ACAGGACC         | GGUCCUGUA | CUCCACCC |
|    | 4250 | GUGGGGUG | CUGAUGA | x   | GAA | AGUACAGG         | CCUGUACUC | CACCCCAC |
| 10 | 4263 | AAACUCUA | CUGAUGA | x   | GAA | AUGGGUGG         | CCACCCAUC | UAGAGUUU |
|    | 4265 | UCAAACUC | CUGAUGA | x   | GAA | <b>AGAUGG</b> GU | ACCCAUCUA | GAGUUUGA |
|    | 4270 | UCGUGUCA | CUGAUGA | X   | GAA | ACUCUAGA         | UCUAGAGUU | UGACACGA |
|    | 4271 | UUCGUGUC | CUGAUGA | X   | GAA | AACUCUAG         | CUAGAGUUU | GACACGAA |
|    | 4284 | CUAGAAAU | CUGAUGA | X   | GAA | AGGCUUCG         | CGAAGCCUU | AUUUCUAG |
| 15 | 4285 | UCUAGAAA | CUGAUGA | X   | GAA | AAGGCUUC         | GAAGCCUUA | UUUCUAGA |
|    | 4287 | CUUCUAGA | CUGAUGA | x   | GAA | AUAAGGCU         | AGCCUUAUU | UCUAGAAG |
|    | 4288 | GCUUCUAG | CUGAUGA | X   | GAA | AAUAAGGC         | GCCUUAUUU | CUAGAAGC |
|    | 4289 | UGCUUCUA | CUGAUGA | X   | GAA | AAAUAAGG         | CCUUAUUUC | UAGAAGCA |
|    | 4291 | UGUGCUUC | CUGAUGA | X   | GAA | AGAAAUAA         | UUAUUUCUA | GAAGCACA |
| 20 | 4305 | GGUAUAAA | CUGAUGA | x   | GAA | ACACAUGU         | ACAUGUGUA | UUUAUACC |
|    | 4307 | GGGGUAUA | CUGAUGA | X   | GAA | AUACACAU         | AUGUGUAUU | UAUACCCC |
|    | 4308 | GGGGGUAU | CUGAUGA | x   | GAA | AAUACACA         | UGUGUAUUU | AUACCCCC |
|    | 4309 | UGGGGGUA | CUGAUGA | X   | GAA | AAAUACAC         | GUGUAUUUA | UACCCCCA |
|    | 4311 | CCUGGGGG | CUGAUGA | X   | GAA | AUAAAUAC         | GUAUUUAUA | CCCCCAGG |
| 25 | 4325 | GCAAAAGC | CUGAUGA | x   | GAA | AGUUUCCU         | AGGAAACUA | GCUUUUGC |
|    | 4329 | ACUGGCAA | CUGAUGA | X   | GAA | AGCUAGUU         | AACUAGCUU | UUGCCAGU |
|    | 4330 | UACUGGCA | CUGAUGA | X   | GAA | AAGCUAGU         | ACUAGCUUU | UGCCAGUA |
|    | 4331 | AUACUGGC | CUGAUGA | X   | GAA | AAAGCUAG         | CUAGCUUUU | GCCAGUAU |
|    | 4338 | AUGCAUAA | CUGAUGA | X   | GAA | ACUGGCAA         | UUGCCAGUA | UUAUGCAU |
| 30 | 4340 | AUAUGCAU | CUGAUGA | X   | GAA | AUACUGGC         | GCCAGUAUU | AUGCAUAU |
|    | 4341 | UAUAUGCA | CUGAUGA | X   | GAA | AAUACUGG         | CCAGUAUUA | UGCAUAUA |
|    | 4347 | AACUUAUA | CUGAUGA | X   | GAA | AUGCAUAA         | UUAUGCAUA | UAUAAGUU |
|    | 4349 | UAAACUUA | CUGAUGA | X   | GAA | AUAUGCAU         | AUGCAUAUA | UAAGUUUA |
|    |      |          |         |     |     |                  |           |          |

|    | 4351 | UGUAAACI | J CUGAUGA | K A | GA. | AUAUAUGC | GCAUAUAU  | A AGUUUAC  |
|----|------|----------|-----------|-----|-----|----------|-----------|------------|
|    | 4355 | AAGGUGUA | CUGAUGA   | X   | GAA | ACUUAUAU | AUAUAAGUI | J UACACCUT |
|    | 4356 | AAAGGUGU | J CUGAUGA | X   | GAA | AACUUAUA | UAUAAGUUT | J ACACCUUT |
|    | 4357 | UAAAGGUG | CUGAUGA   | X   | GAA | AAACUUAU | AUAAGUUU  | A CACCUUU  |
| 5  | 4363 | GAAAGAUA | CUGAUGA   | X   | GAA | AGGUGUAA | UUACACCUI | J UAUCUUUG |
|    | 4364 | GGAAAGAU | CUGAUGA   | X   | GAA | AAGGUGUA | UACACCUUT | AUCUUUCO   |
|    | 4365 | UGGAAAGA | CUGAUGA   | X   | GAA | AAAGGUGU | ACACCUUU  | UCUUUCCA   |
|    | 4367 | CAUGGAAA | CUGAUGA   | X   | GAA | AUAAAGGU | ACCUUUAUC | UUUCCAUG   |
|    | 4369 | CCCAUGGA | CUGAUGA   | X   | GAA | AGAUAAAG | CUUUAUCUU | UCCAUGGG   |
| 10 | 4370 | UCCCAUGG | CUGAUGA   | X   | GAA | AAGAUAAA | UUUAUCUUU | CCAUGGGA   |
|    | 4371 | CUCCCAUG | CUGAUGA   | X   | GAA | AAAGAUAA | UUAUCUUUC | CAUGGGAG   |
|    | 4389 | AUCACAAA | CUGAUGA   | X   | GAA | AGCAGCUG | CAGCUGCUU | UUUGUGAU   |
|    | 4390 | AAUCACAA | CUGAUGA   | X   | GAA | AAGCAGCU | AGCUGCUUU | UUGUGAUU   |
|    | 4391 | AAAUCACA | CUGAUGA   | X   | GAA | AAAGCAGC | GCUGCUUUU | UGUGAUUU   |
| 15 | 4392 | AAAAUCAC | CUGAUGA   | X   | GAA | AAAAGCAG | CUGCUUUUU | GUGAUUUU   |
|    | 4398 | AAAAAUUA | CUGAUGA   | X   | GAA | AUCACAAA | UUUGUGAUU | UUUUUAAU   |
|    | 4399 | UAUUAAAA | CUGAUGA   | X   | GAA | AAUCACAA | UUGUGAUUU | UUUUAAUA   |
|    | 4400 | CUAUUAAA | CUGAUGA   | X   | GAA | AAAUCACA | UGUGAUUUU | UUUAAUAG   |
|    | 4401 | ACUAUUAA | CUGAUGA   | X   | GAA | AAAAUCAC | GUGAUUUUU | UUAAUAGU   |
| 20 | 4402 | CACUAUUA | CUGAUGA   | X   | GAA | AAAAAUCA | UGAUUUUUU | UAAUAGUG   |
|    | 4403 | GCACUAUU | CUGAUGA   | X   | GAA | AAAAAAUC | GAUUUUUUU | AAUAGUGC   |
|    | 4404 | AGCACUAU | CUGAUGA   | x   | GAA | DAAAAAAU | AUUUUUUUA | AUAGUGCU   |
|    | 4407 | AAAAGCAC | CUGAUGA   | X   | GAA | AAAAAUUA | UUUUUAAUA | GUGCUUUU   |
|    | 4413 | AAAAAAA  |           |     |     |          | AUAGUGCUU | טטטטטטטט   |
| 25 | 4414 | ААААААА  | CUGAUGA   | X   | GAA | AAGCACUA | UAGUGCUUU | עטטטטטטט   |
|    | 4415 | САААААА  | CUGAUGA   | X   | GAA | AAAGCACU | AGUGCUUUU | บบบบบบบ    |
|    | 4416 | UCAAAAAA |           |     |     |          | GUGCUUUUU | UUUUUUGA   |
|    | 4417 | GUCAAAAA | CUGAUGA   | X   | GAA | AAAAAGCA | ugcuuuuuu | UUUUUGAC   |
|    | 4418 |          |           |     |     | AAAAAAGC | GCUUUUUUU | UUUUGACU   |
| 30 | 4419 |          |           |     |     | Aaaaaag  | CUUUUUUUU | UUUGACUA   |
|    |      |          |           |     |     | AAAAAAA  |           | UUGACUAA   |
| ٠  | 4421 | GUUAGUCA | CUGAUGA   | X   | GAA | AAAAAAA  | ນນນນນນນນ  | UGACUAAC   |
|    | 4422 | UGUUAGUC | CUGAUGA   | х   | GAA | ААААААА  | บบบบบบบบบ | GACTIAACA  |

|    | 4427 | AUUCUUGU | CUGAUGA | x | GAA | AGUCAAAA | UUUUGACUA | ACAAGAAU |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 4438 | UCUGGAGU | CUGAUGA | x | GAA | ACAUUCUU | AAGAAUGUA | ACUCCAGA |
|    | 4442 | UCUAUCUG | CUGAUGA | x | GAA | AGUUACAU | AUGUAACUC | CAGAUAGA |
|    | 4448 | UAUUUCUC | CUGAUGA | x | GAA | AUCUGGAG | CUCCAGAUA | GAGAAAUA |
| 5  | 4456 | CUUGUCAC | CUGAUGA | X | GAA | AUUUCUCU | AGAGAAAUA | GUGACAAG |
|    | 4476 | UUUAGCAG | CUGAUGA | x | GAA | AGUGUUCU | AGAACACUA | CUGCUAAA |
|    | 4482 | UGAGGAUU | CUGAUGA | x | GAA | AGCAGUAG | CUACUGCUA | AAUCCUCA |
|    | 4486 | AACAUGAG | CUGAUGA | x | GAA | AUUUAGCA | UGCUAAAUC | CUCAUGUU |
|    | 4489 | AGUAACAU | CUGAUGA | x | GAA | AGGAUUUA | UAAAUCCUC | AUGUUACU |
| 10 | 4494 | CACUGAGU | CUGAUGA | x | GAA | ACAUGAGG | CCUCAUGUU | ACUCAGUG |
|    | 4495 | ACACUGAG | CUGAUGA | X | GAA | AACAUGAG | CUCAUGUUA | CUCAGUGU |
|    | 4498 | CUAACACU | CUGAUGA | x | GAA | AGUAACAU | AUGUUACUC | AGUGUUAG |
|    | 4504 | AUUUCUCU | CUGAUGA | x | GAA | ACACUGAG | CUCAGUGUU | AGAGAAAU |
|    | 4505 | GAUUUCUC | CUGAUGA | x | GAA | AACACUGA | UCAGUGUUA | GAGAAAUC |
| 15 | 4513 | UUAGGAAG | CUGAUGA | x | GAA | AUUUCUCU | AGAGAAAUC | CUUCCUAA |
|    | 4516 | GGUUUAGG | CUGAUGA | x | GAA | AGGAUUUC | GAAAUCCUU | CCUAAACC |
|    | 4517 | GGGUUUAG | CUGAUGA | X | GAA | AAGGAUUU | AAAUCCUUC | CUAAACCC |
|    | 4520 | AUUGGGUU | CUGAUGA | x | GAA | AGGAAGGA | UCCUUCCUA | AACCCAAU |
|    | 4533 | GAGCAGGG | CUGAUGA | x | GAA | AGUCAUUG | CAAUGACUU | cccuccuc |
| 20 | 4534 | GGAGCAGG | CUGAUGA | x | GAA | AAGUCAUU | AAUGACUUC | CCUGCUCC |
|    | 4541 | GGGGGUUG | CUGAUGA | x | GAA | AGCAGGGA | UCCCUGCUC | CAACCCCC |
|    | 4557 | CGUGCCCU | CUGAUGA | x | GAA | AGGUGGCG | CGCCACCUC | AGGGCACG |
|    | 4576 | CUCAAUCA | CUGAUGA | x | GAA | ACUGGUCC | GGACCAGUU | UGAUUGAG |
|    | 4577 | CCUCAAUC | CUGAUGA | x | GAA | AACUGGUC | GACCAGUUU | GAUUGAGG |
| 25 | 4581 | AGCUCCUC | CUGAUGA | x | GAA | AUCAAACU | AGUUUGAUU | GAGGAGCU |
|    | 4598 | CAUUGGGU | CUGAUGA | x | GAA | AUCAGUGC | GCACUGAUC | ACCCAAUG |
|    | 4610 | GGGUACGU | CUGAUGA | X | GAA | AUGCAUUG | CAAUGCAUC | ACGUACCC |
|    | 4615 | CAGUGGGG | CUGAUGA | X | GAA | ACGUGAUG | CAUCACGUA | CCCCACUG |
|    | 4664 | CUGGGGCU | CUGAUGA | X | GAA | ACGGGCUU | AAGCCCGUU | AGCCCCAG |
| 30 | 4665 | CCUGGGGC | CUGAUGA | X | GAA | AACGGGCU | AGCCCGUUA | GCCCCAGG |
|    | 4678 | CAGCCAGU | CUGAUGA | x | GAA | AUCCCCUG | CAGGGGAUC | ACUGGCUG |
|    | 4700 | ACUCCCGA | CUGAUGA | X | GAA | AUGUUGCU | AGCAACAUC | UCGGGAGU |
|    | 4702 | GGACUCCC | CUGAUGA | x | GAA | AGAUGUUG | CAACAUCUC | GGGAGUCC |
|    |      |          |         |   |     |          |           |          |

|    | 4709 | UGCUAGAG CUGAUGA X GAA ACUCCCGA | UCGGGAGUC CUCUAGCA |
|----|------|---------------------------------|--------------------|
|    | 4712 | GCCUGCUA CUGAUGA X GAA AGGACUCC | GGAGUCCUC UAGCAGGC |
|    | 4714 | AGGCCUGC CUGAUGA X GAA AGAGGACU | AGUCCUCUA GCAGGCCU |
|    | 4723 | ACAUGUCU CUGAUGA X GAA AGGCCUGC | GCAGGCCUA AGACAUGU |
| 5  | 4802 | GCGUCUCA CUGAUGA X GAA AUUCUUUC | GAAAGAAUU UGAGACGC |
|    | 4803 | UGCGUCUC CUGAUGA X GAA AAUUCUUU | AAAGAAUUU GAGACGCA |
|    | 4840 | GCAUUGCU CUGAUGA X GAA AGCCCCGU | ACGGGGCUC AGCAAUGC |
|    | 4852 | GCCACUGA CUGAUGA X GAA AUGGCAUU | AAUGCCAUU UCAGUGGC |
|    | 4853 | AGCCACUG CUGAUGA X GAA AAUGGCAU | AUGCCAUUU CAGUGGCU |
| 10 | 4854 | AAGCCACU CUGAUGA X GAA AAAUGGCA | UGCCAUUUC AGUGGCUU |
|    | 4862 | GAGCUGGG CUGAUGA X GAA AGCCACUG | CAGUGGCUU CCCAGCUC |
|    | 4863 | AGAGCUGG CUGAUGA X GAA AAGCCACU | AGUGGCUUC CCAGCUCU |
|    | 4870 | AAGGGUCA CUGAUGA X GAA AGCUGGGA | UCCCAGCUC UGACCCUU |
|    | 4878 | AAAUGUAG CUGAUGA X GAA AGGGUCAG | CUGACCCUU CUACAUUU |
| 15 | 4879 | CAAAUGUA CUGAUGA X GAA AAGGGUCA | UGACCCUUC UACAUUUG |
|    | 4881 | CUCAAAUG CUGAUGA X GAA AGAAGGGU | ACCCUUCUA CAUUUGAG |
|    | 4885 | GGCCCUCA CUGAUGA X GAA AUGUAGAA | UUCUACAUU UGAGGGCC |
|    | 4886 | GGGCCCUC CUGAUGA X GAA AAUGUAGA | UCUACAUUU GAGGGCCC |
|    | 4929 | AUCCAGAA CUGAUGA X GAA AUGUCCCC | GGGGACAUU UUCUGGAU |
| 20 | 4930 | AAUCCAGA CUGAUGA X GAA AAUGUCCC | GGGACAUUU UCUGGAUU |
|    | 4931 | GAAUCCAG CUGAUGA X GAA AAAUGUCC | GGACAUUUU CUGGAUUC |
|    | 4932 | AGAAUCCA CUGAUGA X GAA AAAAUGUC | GACAUUUUC UGGAUUCU |
|    | 4938 | CCUCCCAG CUGAUGA X GAA AUCCAGAA | UUCUGGAUU CUGGGAGG |
|    | 4939 | GCCUCCCA CUGAUGA X GAA AAUCCAGA | UCUGGAUUC UGGGAGGC |
| 25 | 4963 | AAAAAAGA CUGAUGA X GAA AUUUGUCC | GGACAAAUA UCUUUUUU |
|    | 4965 | CCAAAAAA CUGAUGA X GAA AUAUUUGU | ACAAAUAUC UUUUUUGG |
|    | 4967 | UUCCAAAA CUGAUGA X GAA AGAUAUUU | AAAUAUCUU UUUUGGAA |
|    | 4968 | GUUCCAAA CUGAUGA X GAA AAGAUAUU | AAUAUCUUU UUUGGAAC |
|    |      | AGUUCCAA CUGAUGA X GAA AAAGAUAU | AUAUCUUUU UUGGAACU |
| 30 |      | UAGUUCCA CUGAUGA X GAA AAAAGAUA | UAUCUUUUU UGGAACUA |
|    | 4971 | UUAGUUCC CUGAUGA X GAA AAAAAGAU | AUCUUUUUU GGAACUAA |
|    | 4978 | AUUUGCUU CUGAUGA X GAA AGUUCCAA | UUGGAACUA AAGCAAAU |
|    | 4987 | AGGUCUAA CUGAUGA X GAA AUUUGCUU | AAGCAAAUU UUAGACCU |
|    |      |                                 |                    |

|    | 4988 | B AAGGUCUA CUGAUGA X GAA AAUUUGCU | AGCAAAUUU UAGACCUU |
|----|------|-----------------------------------|--------------------|
|    | 4989 | AAAGGUCU CUGAUGA X GAA AAAUUUGC   | GCAAAUUUU AGACCUUU |
|    | 4990 | UAAAGGUC CUGAUGA X GAA AAAAUUUG   | CAAAUUUUA GACCUUUA |
|    | 4996 | CAUAGGUA CUGAUGA X GAA AGGUCUAA   | UUAGACCUU UACCUAUG |
| 5  | 4997 | CCAUAGGU CUGAUGA X GAA AAGGUCUA   | UAGACCUUU ACCUAUGG |
|    | 4998 | UCCAUAGG CUGAUGA X GAA AAAGGUCU   | AGACCUUUA CCUAUGGA |
|    | 5002 | CACUUCCA CUGAUGA X GAA AGGUAAAG   | CUUUACCUA UGGAAGUG |
|    | 5013 | GGACAUAG CUGAUGA X GAA ACCACUUC   | GAAGUGGUU CUAUGUCC |
|    | 5014 | UGGACAUA CUGAUGA X GAA AACCACUU   | AAGUGGUUC UAUGUCCA |
| 10 | 5016 | AAUGGACA CUGAUGA X GAA AGAACCAC   | GUGGUUCUA UGUCCAUU |
|    | 5020 | UGAGAAUG CUGAUGA X GAA ACAUAGAA   | UUCUAUGUC CAUUCUCA |
|    | 5024 | CGAAUGAG CUGAUGA X GAA AUGGACAU   | AUGUCCAUU CUCAUUCG |
|    | 5025 | ACGAAUGA CUGAUGA X GAA AAUGGACA   | UGUCCAUUC UCAUUCGU |
|    | 5027 | CCACGAAU CUGAUGA X GAA AGAAUGGA   | UCCAUUCUC AUUCGUGG |
| 15 | 5030 | AUGCCACG CUGAUGA X GAA AUGAGAAU   | AUUCUCAUU CGUGGCAU |
|    | 5031 | CAUGCCAC CUGAUGA X GAA AAUGAGAA   | UUCUCAUUC GUGGCAUG |
|    | 5041 | CAAAUCAA CUGAUGA X GAA ACAUGCCA   | UGGCAUGUU UUGAUUUG |
|    | 5042 | ACAAAUCA CUGAUGA X GAA AACAUGCC   | GGCAUGUUU UGAUUUGU |
|    | 5043 | UACAAAUC CUGAUGA X GAA AAACAUGC   | GCAUGUUUU GAUUUGUA |
| 20 | 5047 | GUGCUACA CUGAUGA X GAA AUCAAAAC   | GUUUUGAUU UGUAGCAC |
|    | 5048 | AGUGCUAC CUGAUGA X GAA AAUCAAAA   | UUUUGAUUU GUAGCACU |
|    | 5051 | CUCAGUGC CUGAUGA X GAA ACAAAUCA   | UGAUUUGUA GCACUGAG |
|    | 5069 | UCAGAGUU CUGAUGA X GAA AGUGCCAC   | GUGGCACUC AACUCUGA |
|    | 5074 | UGGGCUCA CUGAUGA X GAA AGUUGAGU   | ACUCAACUC UGAGCCCA |
| 25 | 5084 | GCCAAAAG CUGAUGA X GAA AUGGGCUC   | GAGCCCAUA CUUUUGGC |
|    | 5087 | GGAGCCAA CUGAUGA X GAA AGUAUGGG   | CCCAUACUU UUGGCUCC |
|    | 5088 | AGGAGCCA CUGAUGA X GAA AAGUAUGG   | CCAUACUUU UGGCUCCU |
|    | 5089 | GAGGAGCC CUGAUGA X GAA AAAGUAUG   | CAUACUUUU GGCUCCUC |
|    | 5094 | UACUAGAG CUGAUGA X GAA AGCCAAAA   | UUUUGGCUC CUCUAGUA |
| 30 | 5097 | UCUUACUA CUGAUGA X GAA AGGAGCCA   | UGGCUCCUC UAGUAAGA |
|    | 5099 | CAUCUUAC CUGAUGA X GAA AGAGGAGC   | GCUCCUCUA GUAAGAUG |
|    | 5102 | GUGCAUCU CUGAUGA X GAA ACUAGAGG   | CCUCUAGUA AGAUGCAC |
|    | 5119 | CUCUGGCU CUGAUGA X GAA AGUUUUCA   | UGAAAACUU AGCCAGAG |

|    | 5120 | ACUCUGGC | CUGAUGA | . х | GAA | AAGUUUUC | GAAAACUUA GCCAGAGU |
|----|------|----------|---------|-----|-----|----------|--------------------|
|    | 5129 | GACAACCU | CUGAUGA | X   | GAA | ACUCUGGC | GCCAGAGUU AGGUUGUC |
|    | 5130 | AGACAACC | CUGAUGA | X   | GAA | AACUCUGG | CCAGAGUUA GGUUGUCU |
|    | 5134 | CUGGAGAC | CUGAUGA | X   | GAA | ACCUAACU | AGUUAGGUU GUCUCCAG |
| 5  | 5137 | GGCCUGGA | CUGAUGA | X   | GAA | ACAACCUA | UAGGUUGUC UCCAGGCC |
|    | 5139 | AUGGCCUG | CUGAUGA | X   | GAA | AGACAACC | GGUUGUCUC CAGGCCAU |
|    | 5156 | UUCAGUGU | CUGAUGA | X   | GAA | AGGCCAUC | GAUGGCCUU ACACUGAA |
|    | 5157 | UUUCAGUG | CUGAUGA | X   | GAA | AAGGCCAU | AUGGCCUUA CACUGAAA |
|    | 5170 | UAGAAUGU | CUGAUGA | X   | GAA | ACAUUUUC | GAAAAUGUC ACAUUCUA |
| 10 | 5175 | CAAAAUAG | CUGAUGA | X   | GAA | AUGUGACA | UGUCACAUU CUAUUUUG |
|    | 5176 | CCAAAAUA | CUGAUGA | X   | GAA | AAUGUGAC | GUCACAUUC UAUUUUGG |
|    | 5178 | ACCCAAAA | CUGAUGA | X   | GAA | AGAAUGUG | CACAUUCUA UUUUGGGU |
|    | 5180 | AUACCCAA | CUGAUGA | x   | GAA | AUAGAAUG | CAUUCUAUU UUGGGUAU |
|    | 5181 | AAUACCCA | CUGAUGA | x   | GAA | AAUAGAAU | AUUCUAUUU UGGGUAUU |
| 15 | 5182 | UAAUACCC | CUGAUGA | X   | GAA | AAAUAGAA | UUCUAUUUU GGGUAUUA |
|    | 5187 | UAUAUUAA | CUGAUGA | X   | GAA | ACCCAAAA | UUUUGGGUA UUAAUAUA |
|    | 5189 | UAUAUAUU | CUGAUGA | X   | GAA | AUACCCAA | UUGGGUAUU AAUAUAUA |
|    | 5190 | CUAUAUAU | CUGAUGA | X   | GAA | AAUACCCA | UGGGUAUUA AUAUAUAG |
|    | 5193 | GGACUAUA | CUGAUGA | X   | GAA | AUUAAUAC | GUAUUAAUA UAUAGUCC |
| 20 | 5195 | CUGGACUA | CUGAUGA | X   | GAA | UAAUUAAU | AUUAAUAUA UAGUCCAG |
|    | 5197 | GUCUGGAC | CUGAUGA | X   | GAA | AUAUAUUA | UAAUAUAUA GUCCAGAC |
|    | 5200 | AGUGUCUG | CUGAUGA | X   | GAA | ACUAUAUA | UAUAUAGUC CAGACACU |
|    | 5209 | AUUGAGUU | CUGAUGA | X   | GAA | AGUGUCUG | CAGACACUU AACUCAAU |
|    | 5210 | AAUUGAGU | CUGAUGA | X   | GAA | AAGUGUCU | AGACACUUA ACUCAAUU |
| 25 | 5214 | AAGAAAUU | CUGAUGA | X   | GAA | AGUUAAGU | ACUUAACUC AAUUUCUU |
|    | 5218 | UACCAAGA | CUGAUGA | X   | GAA | AUUGAGUU | AACUCAAUU UCUUGGUA |
|    | 5219 | AUACCAAG | CUGAUGA | X   | GAA | AAUUGAGU | ACUCAAUUU CUUGGUAU |
|    | 5220 | AAUACCAA | CUGAUGA | X   | GAA | AAAUUGAG | CUCAAUUUC UUGGUAUU |
|    | 5222 | AUAAUACC | CUGAUGA | X   | GAA | AGAAAUUG | CAAUUUCUU GGUAUUAU |
| 30 | 5226 | CAGAAUAA | CUGAUGA | X   | GAA | ACCAAGAA | UUCUUGGUA UUAUUCUG |
|    | 5228 | AACAGAAU | CUGAUGA | X   | GAA | AUACCAAG | CUUGGUAUU AUUCUGUU |
|    | 5229 | AAACAGAA | CUGAUGA | X   | GAA | AAUACCAA | UUGGUAUUA UUCUGUUU |
|    | 5231 | CAAAACAG | CUGAUGA | X   | GAA | AUAAUACC | GGUAUUAUU CUGUUUUG |
|    |      |          |         |     |     |          |                    |

|    | 5232 | GCAAAACA | CUGAUGA | . > | GA  | AAUAAUAC   | GUAUUAUUC UGUUUUGC |
|----|------|----------|---------|-----|-----|------------|--------------------|
|    | 5236 | CUGUGCAA | CUGAUGA | X   | GA, | A ACAGAAUA | UAUUCUGUU UUGCACAG |
|    | 5237 | ACUGUGCA | CUGAUGA | . X | GAA | AACAGAAU   | AUUCUGUUU UGCACAGU |
|    | 5238 | AACUGUGC | CUGAUGA | . х | GAA | AAACAGAA   | UUCUGUUUU GCACAGUU |
| 5  | 5246 | UCACAACU | CUGAUGA | . X | GAA | ACUGUGCA   | UGCACAGUU AGUUGUGA |
|    | 5247 | UUCACAAC | CUGAUGA | Х   | GAA | AACUGUGC   | GCACAGUUA GUUGUGAA |
|    | 5250 | UCUUUCAC | CUGAUGA | Х   | GAA | ACUAACUG   | CAGUUAGUU GUGAAAGA |
|    | 5284 | CUCCUCAG | CUGAUGA | X   | GAA | ACUGCAUU   | AAUGCAGUC CUGAGGAG |
|    | 5296 | AUGGAGAA | CUGAUGA | X   | GAA | ACUCUCCU   | AGGAGAGUU UUCUCCAU |
| 10 | 5297 | UAUGGAGA | CUGAUGA | X   | GAA | AACUCUCC   | GGAGAGUUU UCUCCAUA |
|    | 5298 | AUAUGGAG | CUGAUGA | X   | GAA | AAACUCUC   | GAGAGUUUU CUCCAUAU |
|    | 5299 | GAUAUGGA | CUGAUGA | X   | GAA | AAAACUCU   | AGAGUUUUC UCCAUAUC |
|    | 5301 | UUGAUAUG | CUGAUGA | X   | GAA | AGAAAACU   | AGUUUUCUC CAUAUCAA |
|    | 5305 | CGUUUUGA | CUGAUGA | X   | GAA | AUGGAGAA   | UUCUCCAUA UCAAAACG |
| 15 | 5307 | CUCGUUUU | CUGAUGA | X   | GAA | AUAUGGAG   | CUCCAUAUC AAAACGAG |
|    | 5336 | ACCUUAUU | CUGAUGA | X   | GAA | ACCUUUUU   | AAAAAGGUC AAUAAGGU |
|    | 5340 | CUUGACCU | CUGAUGA | X   | GAA | AUUGACCU   | AGGUCAAUA AGGUCAAG |
|    | 5345 | CUUCCCUU | CUGAUGA | X   | GAA | ACCUUAUU   | AAUAAGGUC AAGGGAAG |
|    | 5361 | GGUAUAGA | CUGAUGA | X   | GAA | ACGGGGUC   | GACCCCGUC UCUAUACC |
| 20 | 5363 | UUGGUAUA | CUGAUGA | X   | GAA | AGACGGGG   | CCCCGUCUC UAUACCAA |
|    | 5365 | GGUUGGUA | CUGAUGA | X   | GAA | AGAGACGG   | CCGUCUCUA UACCAACC |
|    | 5367 | UUGGUUGG | CUGAUGA | X   | GAA | AUAGAGAC   | GUCUCUAUA CCAACCAA |
|    | 5382 | UGUUGGUG | CUGAUGA | X   | GAA | AUUGGUUU   | AAACCAAUU CACCAACA |
|    | 5383 | GUGUUGGU | CUGAUGA | X   | GAA | AAUUGGUU   | AACCAAUUC ACCAACAC |
| 25 | 5395 | UGGGUCCC | CUGAUGA | X   | GAA | ACUGUGUU   | AACACAGUU GGGACCCA |
|    | 5417 | ACGUGACU | CUGAUGA | X   | GAA | ACUUCCUG   | CAGGAAGUC AGUCACGU |
|    | 5421 | GGAAACGU | CUGAUGA | X   | GAA | ACUGACUU   | AAGUCAGUC ACGUUUCC |
|    | 5426 | GAAAAGGA | CUGAUGA | X   | GAA | ACGUGACU   | AGUCACGUU UCCUUUUC |
|    | 5427 |          |         |     |     | AACGUGAC   | GUCACGUUU CCUUUUCA |
| 30 | 5428 |          |         |     |     | AAACGUGA   | UCACGUUUC CUUUUCAU |
|    | 5431 |          |         |     |     | AGGAAACG   |                    |
|    | 5432 |          |         |     |     | AAGGAAAC   | GUUUCCUUU UCAUUUAA |
|    | 5433 | AUUAAAUG | CUGAUGA | X   | GAA | AAAGGAAA   | UUUCCUUUU CAUUUAAU |

|    | 5434 | CAUUAAÄU | CUGAUGA | X   | GAZ | A AAAAGGAA | UUCCUUUUC AUUUAAU  |
|----|------|----------|---------|-----|-----|------------|--------------------|
|    | 5437 | CCCCAUUA | CUGAUGA | X   | GAZ | AUGAAAAG   | CUUUUCAUU UAAUGGGO |
|    | 5438 | UCCCCAUU | CUGAUGA | X   | GAZ | AAUGAAAA   | UUUUCAUUU AAUGGGGA |
|    | 5439 | AUCCCCAU | CUGAUGA | . х | GAA | AAAUGAAA   | UUUCAUUUA AUGGGGAU |
| 5  | 5448 | GAUAGUGG | CUGAUGA | . х | GAA | AUCCCCAU   | AUGGGGAUU CCACUAUC |
|    | 5449 | AGAUAGUG | CUGAUGA | . x | GAA | AAUCCCCA   | UGGGGAUUC CACUAUCU |
|    | 5454 | GUGUGAGA | CUGAUGA | X   | GAA | AGUGGAAU   | AUUCCACUA UCUCACAC |
|    | 5456 | UAGUGUGA | CUGAUGA | X   | GAA | AUAGUGGA   | UCCACUAUC UCACACUA |
|    | 5458 | AUUAGUGU | CUGAUGA | X   | GAA | AGAUAGUG   | CACUAUCUC ACACUAAU |
| 10 | 5464 | UUUCAGAU | CUGAUGA | X   | GAA | AGUGUGAG   | CUCACACUA AUCUGAAA |
|    | 5467 | UCCUUUCA | CUGAUGA | X   | GAA | AUUAGUGU   | ACACUAAUC UGAAAGGA |
|    | 5489 | CGCCAGCU | CUGAUGA | X   | GAA | AUGCUCUU   | AAGAGCAUU AGCUGGCG |
| -  | 5490 | GCGCCAGC | CUGAUGA | x   | GAA | AAUGCUCU   | AGAGCAUUA GCUGGCGC |
|    | 5501 | GUGCUUAA | CUGAUGA | X   | GAA | AUGCGCCA   | UGGCGCAUA UUAAGCAC |
| 15 | 5503 | AAGUGCUU | CUGAUGA | X   | GAA | AUAUGCGC   | GCGCAUAUU AAGCACUU |
|    | 5504 | AAAGUGCU | CUGAUGA | X   | GAA | AAUAUGCG   | CGCAUAUUA AGCACUUU |
|    | 5511 | GGAGCUUA | CUGAUGA | X   | GAA | AGUGCUUA   | UAAGCACUU UAAGCUCC |
|    | 5512 | AGGAGCUU | CUGAUGA | x   | GAA | AAGUGCUU   | AAGCACUUU AAGCUCCU |
|    | 5513 | AAGGAGCU | CUGAUGA | x   | GAA | AAAGUGCU   | AGCACUUUA AGCUCCUU |
| 20 | 5518 | UACUCAAG | CUGAUGA | x   | GAA | AGCUUAAA   | UUUAAGCUC CUUGAGUA |
|    | 5521 | UUUUACUC | CUGAUGA | X   | GAA | AGGAGCUU   | AAGCUCCUU GAGUAAAA |
|    | 5526 | CACCUUUU | CUGAUGA | X   | GAA | ACUCAAGG   | CCUUGAGUA AAAAGGUG |
|    | 5537 | AAAUUACA | CUGAUGA | X   | GAA | ACCACCUU   | AAGGUGGUA UGUAAUUU |
|    | 5541 | GCAUAAAU | CUGAUGA | X   | GAA | ACAUACCA   | UGGUAUGUA AUUUAUGC |
| 25 | 5544 | CUUGCAUA | CUGAUGA | X   | GAA | AUUACAUA   | UAUGUAAUU UAUGCAAG |
|    | 5545 | CCUUGCAU | CUGAUGA | X   | GAA | AAUUACAU   | AUGUAAUUU AUGCAAGG |
|    | 5546 | ACCUUGCA | CUGAUGA | X   | GAA | AAAUUACA   | UGUAAUUUA UGCAAGGU |
|    | 5555 | UGGAGAAA | CUGAUGA | x   | GAA | ACCUUGCA   | UGCAAGGUA UUUCUCCA |
|    | 5557 | ACUGGAGA | CUGAUGA | x   | GAA | AUACCUUG   | CAAGGUAUU UCUCCAGU |
| 30 | 5558 | AACUGGAG | CUGAUGA | X   | GAA | AAUACCUU   | AAGGUAUUU CUCCAGUU |
|    | 5559 | CAACUGGA | CUGAUGA | X   | GAA | AAAUACCU   | AGGUAUUUC UCCAGUUG |
|    | 5561 | CCCAACUG | CUGAUGA | X   | GAA | AGAAAUAC   | GUAUUUCUC CAGUUGGG |
|    | 5566 | UGAGUCCC | CUGAUGA | X   | GAA | ACUGGAGA   | UCUCCAGUU GGGACUCA |
|    |      |          |         |     |     |            |                    |

PCT/US96/17480 WO 97/15662

|    | 5573 | AAUAUCCU | CUGAUGA | X | GAA | AGUCCCAA | UUGGGACU  | AGGAUAUU |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 5579 | UUAACUAA | CUGAUGA | X | GAA | AUCCUGAG | CUCAGGAUA | UUAGUUAA |
|    | 5581 | CAUUAACU | CUGAUGA | X | GAA | AUAUCCUG | CAGGAUAUU | AGUUAAUG |
|    | 5582 | UCAUUAAC | CUGAUGA | X | GAA | AAUAUCCU | AGGAUAUUA | GUUAAUGA |
| 5  | 5585 | GGCUCAUU | CUGAUGA | x | GAA | ACUAAUAU | AUAUUAGUU | AAUGAGCC |
|    | 5586 | UGGCUCAU | CUGAUGA | x | GAA | AACUAAUA | UAUUAGUUA | AUGAGCCA |
|    | 5596 | CUUCUAGU | CUGAUGA | x | GAA | AUGGCUCA | UGAGCCAUC | ACUAGAAG |
|    | 5600 | טטטטטטט  | CUGAUGA | x | GAA | AGUGAUGG | CCAUCACUA | GAAGAAAA |
|    | 5615 | CAGUUGAA | CUGAUGA | x | GAA | AUGGGCUU | AAGCCCAUU | UUCAACUG |
| 10 | 5616 | GCAGUUGA | CUGAUGA | X | GAA | AAUGGGCU | AGCCCAUUU | UCAACUGC |
|    | 5617 | AGCAGUUG | CUGAUGA | X | GAA | AAAUGGGC | GCCCAUUUU | CAACUGCU |
|    | 5618 | AAGCAGUU | CUGAUGA | x | GAA | AAAAUGGG | CCCAUUUUC | AACUGCUU |
|    | 5626 | AAGUUUCA | CUGAUGA | x | GAA | AGCAGUUG | CAACUGCUU | UGAAACUU |
|    | 5627 | CAAGUUUC | CUGAUGA | x | GAA | AAGCAGUU | AACUGCUUU | GAAACUUG |
| 15 | 5634 | CCCCAGGC | CUGAUGA | x | GAA | AGUUUCAA | UUGAAACUU | GCCUGGGG |
|    | 5644 | CAUGCUCA | CUGAUGA | x | GAA | ACCCCAGG | CCUGGGGUC | UGAGCAUG |
|    | 5661 | UGUCUCCC | CUGAUGA | x | GAA | AUUCCCAU | AUGGGAAUA | GGGAGACA |
|    | 5674 | cccuuucc | CUGAUGA | X | GAA | ACCCUGUC | GACAGGGUA | GGAAAGGG |
|    | 5688 | CUGAAGAG | CUGAUGA | X | GAA | AGGCGCCC | GGGCGCCUA | CUCUUCAG |
| 20 | 5691 | ACCCUGAA | CUGAUGA | X | GAA | AGUAGGCG | CGCCUACUC | UUCAGGGU |
|    | 5693 | AGACCCUG | CUGAUGA | x | GAA | AGAGUAGG | CCUACUCUU | CAGGGUCU |
|    | 5694 | UAGACCCU | CUGAUGA | x | GAA | AAGAGUAG | CUACUCUUC | AGGGUCUA |
|    | 5700 | GAUCUUUA | CUGAUGA | x | GAA | ACCCUGAA | UUCAGGGUC | UAAAGAUC |
|    | 5702 | UUGAUCUU | CUGAUGA | X | GAA | AGACCCUG | CAGGGUCUA | AAGAUCAA |
| 25 | 5708 | GCCCACUU | CUGAUGA | x | GAA | AUCUUUAG | CUAAAGAUC | AAGUGGGC |
|    | 5719 | AGCGAUCC | CUGAUGA | X | GAA | AGGCCCAC | GUGGGCCUU | GGAUCGCU |
|    | 5724 | AGCUUAGC | CUGAUGA | X | GAA | AUCCAAGG | CCUUGGAUC | GCUAAGCU |
|    | 5728 | AGCCAGCU | CUGAUGA | X | GAA | AGCGAUCC | GGAUCGCUA | AGCUGGCU |
|    | 5737 | AUCAAACA | CUGAUGA | X | GAA | AGCCAGCU | AGCUGGCUC | UGUUUGAU |
| 30 | 5741 | UAGCAUCA | CUGAUGA | X | GAA | ACAGAGCC | GGCUCUGUU | UGAUGCUA |
|    | 5742 | AUAGCAUC | CUGAUGA | X | GAA | AACAGAGC | GCUCUGUUU | GAUGCUAU |
|    | 5749 | UGCAUAAA | CUGAUGA | X | GAA | AGCAUCAA | UUGAUGCUA | UUUAUGCA |
|    | 5751 | CUUGCAUA | CUGAUGA | x | GAA | AUAGCAUC | GAUGCUAUU | UAUGCAAG |

|    | 5752 | ACUUGCAU | CUGAUGA | X | GAA | AAUAGCAU | AUGCUAUUU | AUGCAAGU |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 5753 | AACUUGCA | CUGAUGA | X | GAA | AAAUAGCA | UGCUAUUUA | UGCAAGUU |
|    | 5761 | UAGACCCU | CUGAUGA | x | GAA | ACUUGCAU | AUGCAAGUU | AGGGUCUA |
|    | 5762 | AUAGACCC | CUGAUGA | x | GAA | AACUUGCA | UGCAAGUUA | GGGUCUAU |
| 5  | 5767 | AAUACAUA | CUGAUGA | x | GAA | ACCCUAAC | GUUAGGGUC | UAUGUAUU |
|    | 5769 | UAAAUACA | CUGAUGA | х | GAA | AGACCCUA | UAGGGUCUA | UGUAUUUA |
|    | 5773 | AUCCUAAA | CUGAUGA | x | GAA | ACAUAGAC | GUCUAUGUA | UUUAGGAU |
|    | 5775 | GCAUCCUA | CUGAUGA | x | GAA | AUACAUAG | CUAUGUAUU | UAGGAUGC |
|    | 5776 | CGCAUCCU | CUGAUGA | x | GAA | AAUACAUA | UAUGUAUUU | AGGAUGCG |
| 10 | 5777 | GCGCAUCC | CUGAUGA | x | GAA | AAAUACAU | AUGUAUUUA | GGAUGCGC |
|    | 5788 | CUGAAGAG | CUGAUGA | X | GAA | AGGCGCAU | AUGCGCCUA | CUCUUCAG |
|    | 5791 | ACCCUGAA | CUGAUGA | X | GAA | AGUAGGCG | CGCCUACUC | UUCAGGGU |
|    | 5793 | AGACCCUG | CUGAUGA | X | GAA | AGAGUAGG | CCUACUCUU | CAGGGUCU |
|    | 5794 | UAGACCCU | CUGAUGA | X | GAA | AAGAGUAG | CUACUCUUC | AGGGUCUA |
| 15 | 5800 | GAUCUUUA | CUGAUGA | X | GAA | ACCCUGAA | UUCAGGGUC | UAAAGAUC |
|    | 5802 | UUGAUCUU | CUGAUGA | X | GAA | AGACCCUG | CAGGGUCUA | AAGAUCAA |
|    | 5808 | GCCCACUU | CUGAUGA | x | GAA | AUCUUUAG | CUAAAGAUC | AAGUGGGC |
|    | 5819 | AGCGAUCC | CUGAUGA | X | GAA | AGGCCCAC | GUGGGCCUU | GGAUCGCU |
|    | 5824 | AGCUUAGC | CUGAUGA | X | GAA | AUCCAAGG | CCUUGGAUC | GCUAAGCU |
| 20 | 5828 | AGCCAGCU | CUGAUGA | x | GAA | AGCGAUCC | GGAUCGCUA | AGCUGGCU |
|    | 5837 | AUCAAACA | CUGAUGA | X | GAA | AGCCAGCU | AGCUGGCUC | UGUUUGAU |
|    | 5841 | UAGCAUCA | CUGAUGA | X | GAA | ACAGAGCC | GGCUCUGUU | UGAUGCUA |
|    | 5842 | AUAGCAUC | CUGAUGA | x | GAA | AACAGAGC | GCUCUGUUU | GAUGCUAU |
|    | 5849 | UGCAUAAA | CUGAUGA | X | GAA | AGCAUCAA | UUGAUGCUA | UUUAUGCA |
| 25 | 5851 | CUUGCAUA | CUGAUGA | X | GAA | AUAGCAUC | GAUGCUAUU | UAUGCAAG |
|    | 5852 | ACUUGCAU | CUGAUGA | X | GAA | AAUAGCAU | AUGCUAUUU | AUGCAAGU |
|    | 5853 | AACUUGCA | CUGAUGA | X | GAA | AAAUAGCA | UGCUAUUUA | UGCAAGUU |
|    | 5861 | UAGACCCU | CUGAUGA | X | GAA | ACUUGCAU | AUGCAAGUU | AGGGUCUA |
|    | 5862 | AUAGACCC | CUGAUGA | x | GAA | AACUUGCA | UGCAAGUUA | GGGUCUAU |
| 30 | 5867 | AAUACAUA | CUGAUGA | X | GAA | ACCCUAAC | GUUAGGGUC | UAUGUAUU |
|    | 5869 | UAAAUACA | CUGAUGA | X | GAA | AGACCCUA | UAGGGUCUA | UGUAUUUA |
|    | 5873 | AUCCUAAA | CUGAUGA | x | GAÀ | ACAUAGAC | GUCUAUGUA | UUUAGGAU |
|    | 5875 | ACAUCCUA | CUGAUGA | x | GAA | AUACAUAG | CUAUGUAUU | UAGGAUGU |

|    | 5876        | GACAUCCU | CUGAUGA | X | GAA | AAUACAUA | UAUGUAUUU | AGGAUGUC |
|----|-------------|----------|---------|---|-----|----------|-----------|----------|
|    | 5877        | AGACAUCC | CUGAUGA | X | GAA | AAAUACAU | AUGUAUUUA | GGAUGUCU |
|    | 5884        | AAGGUGCA | CUGAUGA | X | GAA | ACAUCCUA | UAGGAUGUC | UGCACCUU |
|    | 5892        | GGCUGCAG | CUGAUGA | X | GAA | AGGUGCAG | CUGCACCUU | CUGCAGCC |
| 5  | 5893        | UGGCUGCA | CUGAUGA | X | GAA | AAGGUGCA | UGCACCUUC | UGCAGCCA |
|    | 5904        | CAGCUUCU | CUGAUGA | x | GAA | ACUGGCUG | CAGCCAGUC | AGAAGCUG |
|    | 5930        | GAAGCAGC | CUGAUGA | X | GAA | AUCCACUG | CAGUGGAUU | GCUGCUUC |
|    | 5937        | UCCCCAAG | CUGAUGA | x | GAA | AGCAGCAA | UUGCUGCUU | CUUGGGGA |
|    | 5938        | CUCCCCAA | CUGAUGA | X | GAA | AAGCAGCA | ugcugcuuc | UUGGGGAG |
| 10 | 5940        | UUCUCCCC | CUGAUGA | X | GAA | AGAAGCAG | CUGCUUCUU | GGGGAGAA |
|    | 5953        | AGGAAGCA | CUGAUGA | X | GAA | ACUCUUCU | AGAAGAGUA | UGCUUCCU |
|    | 5958        | AUAAAAGG | CUGAUGA | x | GAA | AGCAUACU | AGUAUGCUU | CCUUUUAU |
|    | 5959        | GAUAAAAG | CUGAUGA | x | GAA | AAGCAUAC | GUAUGCUUC | CUUUUAUC |
|    | 5962        | AUGGAUAA | CUGAUGA | x | GAA | AGGAAGCA | ugcuuccuu | UUAUCCAU |
| 15 | 5963        | CAUGGAUA | CUGAUGA | x | GAA | AAGGAAGC | GCUUCCUUU | UAUCCAUG |
|    | 5964        | ACAUGGAU | CUGAUGA | X | GAA | AAAGGAAG | cuuccuuuu | AUCCAUGU |
|    | 5965        | UACAUGGA | CUGAUGA | X | GAA | AAAAGGAA | UUCCUUUUA | UCCAUGUA |
|    | 5967        | AUUACAUG | CUGAUGA | X | GAA | AUAAAAGG | CCUUUUAUC | CAUGUAAU |
|    | 5973        | AGUUAAAU | CUGAUGA | x | GAA | ACAUGGAU | AUCCAUGUA | AUUUAACU |
| 20 | 5976        | UACAGUUA | CUGAUGA | x | GAA | AUUACAUG | CAUGUAAUU | UAACUGUA |
|    | 5977        | CUACAGUU | CUGAUGA | X | GAA | AAUUACAU | AUGUAAUUU | AACUGUAG |
|    | 5978        | UCUACAGU | CUGAUGA | X | GAA | AAAUUACA | UGUAAUUUA | ACUGUAGA |
|    | 5984        | UCAGGUUC | CUGAUGA | X | GAA | ACAGUUAA | UUAACUGUA | GAACCUGA |
|    | 5996        | GUUACUUA | CUGAUGA | X | GAA | AGCUCAGG | CCUGAGCUC | UAAGUAAC |
| 25 | 5998        | CGGUUACU | CUGAUGA | X | GAA | AGAGCUCA | UGAGCUCUA | AGUAACCG |
|    | 6002        | UCUUCGGU | CUGAUGA | x | GAA | ACUUAGAG | CUCUAAGUA | ACCGAAGA |
|    | 6015        | CAGAGGCA | CUGAUGA | X | GAA | ACAUUCUU | AAGAAUGUA | UGCCUCUG |
|    | 6021        | UAAGAACA | CUGAUGA | x | GAA | AGGCAUAC | GUAUGCCUC | UGUUCUUA |
|    | 6025        | CACAUAAG | CUGAUGA | X | GAA | ACAGAGGC | GCCUCUGUU | CUUAUGUG |
| 30 | 6026        | GCACAUAA | CUGAUGA | X | GAA | AACAGAGG | CCUCUGUUC | UUAUGUGC |
|    | 6028        | UGGCACAU | CUGAUGA | X | GAA | AGAACAGA | UCUGUUCUU | AUGUGCCA |
|    | <b>~029</b> | GUGGCACA | CUGAUGA | X | GAA | AAGAACAG | CUGUUCUUA | UGUGCCAC |
|    | 6040        | UAAACAAG | CUGAUGA | x | GAA | AUGUGGCA | UGCCACAUC | CUUGUUUA |

|    | 6043 | CUUUAAAC | CUGAUGA | X | GAA | AGGAUGUG | CACAUCCUU GUUUAAAG |
|----|------|----------|---------|---|-----|----------|--------------------|
|    | 6046 | AGCCUUUA | CUGAUGA | X | GAA | ACAAGGAU | AUCCUUGUU UAAAGGCU |
|    | 6047 | GAGCCUUU | CUGAUGA | x | GAA | AACAAGGA | UCCUUGUUU AAAGGCUC |
|    | 6048 | AGAGCCUU | CUGAUGA | x | GAA | AAACAAGG | CCUUGUUUA AAGGCUCU |
| 5  | 6055 | CAUACAGA | CUGAUGA | X | GAA | AGCCUUUA | UAAAGGCUC UCUGUAUG |
|    | 6057 | UUCAUACA | CUGAUGA | x | GAA | AGAGCCUU | AAGGCUCUC UGUAUGAA |
|    | 6061 | UCUCUUCA | CUGAUGA | x | GAA | ACAGAGAG | CUCUCUGUA UGAAGAGA |
|    | 6079 | GUGCUGAU | CUGAUGA | X | GAA | ACGGUCCC | GGGACCGUC AUCAGCAC |
|    | 6082 | AAUGUGCU | CUGAUGA | X | GAA | AUGACGGU | ACCGUCAUC AGCACAUU |
| 10 | 6090 | CACUAGGG | CUGAUGA | x | GAA | AUGUGCUG | CAGCACAUU CCCUAGUG |
|    | 6091 | UCACUAGG | CUGAUGA | X | GAA | AAUGUGCU | AGCACAUUC CCUAGUGA |
|    | 6095 | AGGCUCAC | CUGAUGA | x | GAA | AGGGAAUG | CAUUCCCUA GUGAGCCU |
|    | 6104 | GGAGCCAG | CUGAUGA | x | GAA | AGGCUCAC | GUGAGCCUA CUGGCUCC |
|    | 6111 | GCUGCCAG | CUGAUGA | x | GAA | AGCCAGUA | UACUGGCUC CUGGCAGC |
| 15 | 6124 | UUCCACAA | CUGAUGA | x | GAA | AGCCGCUG | CAGCGGCUU UUGUGGAA |
|    | 6125 | CUUCCACA | CUGAUGA | X | GAA | AAGCCGCU | AGCGGCUUU UGUGGAAG |
|    | 6126 | UCUUCCAC | CUGAUGA | X | GAA | AAAGCCGC | GCGGCUUUU GUGGAAGA |
|    | 6137 | UGGCUAGU | CUGAUGA | x | GAA | AGUCUUCC | GGAAGACUC ACUAGCCA |
|    | 6141 | CONCREC  | CUGAUGA | x | GAA | AGUGAGUC | GACUCACUA GCCAGAAG |
| 20 | 6166 | GUGGAGAG | CUGAUGA | x | GAA | ACUGUCCC | GGGACAGUC CUCUCCAC |
|    | 6169 | UUGGUGGA | CUGAUGA | X | GAA | AGGACUGU | ACAGUCCUC UCCACCAA |
|    | 6171 | UCUUGGUG | CUGAUGA | X | GAA | AGAGGACU | AGUCCUCUC CACCAAGA |
|    | 6181 | UGGAUUUA | CUGAUGA | X | GAA | AUCUUGGU | ACCAAGAUC UAAAUCCA |
|    | 6183 | UUUGGAUU | CUGAUGA | X | GAA | AGAUCUUG | CAAGAUCUA AAUCCAAA |
| 25 | 6187 | UUUGUUUG | CUGAUGA | X | GAA | AUUUAGAU | AUCUAAAUC CAAACAAA |
|    | 6204 | UCUGGCUC | CUGAUGA | x | GAA | AGCCUGCU | AGCAGGCUA GAGCCAGA |
|    | 6226 | ACAACAAA | CUGAUGA | X | GAA | AUUUGUCC | GGACAAAUC UUUGUUGU |
|    | 6228 | GAACAACA | CUGAUGA | X | GAA | AGAUUUGU | ACAAAUCUU UGUUGUUC |
|    | 6229 | GGAACAAC | CUGAUGA | X | GAA | AAGAUUUG | CAAAUCUUU GUUGUUCC |
| 30 | 6232 | AGAGGAAC | CUGAUGA | X | GAA | ACAAAGAU | AUCUUUGUU GUUCCUCU |
|    | 6235 | AGAAGAGG | CUGAUGA | X | GAA | ACAACAAA | טטטפטטפטט ככטכטטכט |
|    | 6236 | AAGAAGAG | CUGAUGA | X | GAA | AACAACAA | טטפטטפטטכ כטכטטכטט |
|    | 6239 | GUAAAGAA | CUGAUGA | x | GAA | AGGAACAA | UUGUUCCUC UUCUUUAC |

|    | 6241 | GUGUAAA   | CUGAUGA | K A | GAA | AGAGGAAC | GUUCCUCUU CUUUACAC |
|----|------|-----------|---------|-----|-----|----------|--------------------|
|    | 6242 | UGUGUAA   | CUGAUGA | X   | GAZ | AAGAGGAA | UUCCUCUUC UUUACACA |
|    | 6244 | UAUGUGUA  | CUGAUGA | X   | GAA | AGAAGAGG | CCUCUUCUU UACACAUA |
|    | 6245 | GUAUGUGU  | CUGAUGA | X.  | GAA | AAGAAGAG | CUCUUCUUU ACACAUAC |
| 5  | 6246 | CGUAUGUG  | CUGAUGA | X   | GAA | AAAGAAGA | UCUUCUUUA CACAUACG |
|    | 6252 | GGUUUGCG  | CUGAUGA | X   | GAA | AUGUGUAA | UUACACAUA CGCAAACC |
|    | 6280 | AUUUUAUAA | CUGAUGA | X   | GAA | AUUGCCAG | CUGGCAAUU UUAUAAAU |
|    | 6281 | GAUUUAUA  | CUGAUGA | X   | GAA | AAUUGCCA | UGGCAAUUU UAUAAAUC |
|    | 6282 | UGAUUUAU  | CUGAUGA | X   | GAA | AAAUUGCC | GGCAAUUUU AUAAAUCA |
| 10 | 6283 | CUGAUUUA  | CUGAUGA | X   | GAA | AAAAUUGC | GCAAUUUUA UAAAUCAG |
|    | 6285 | ACCUGAUU  | CUGAUGA | X   | GAA | AUAAAAUU | AAUUUUAUA AAUCAGGU |
|    | 6289 | AGUUACCU  | CUGAUGA | x   | GAA | AUUUAUAA | UUAUAAAUC AGGUAACU |
|    | 6294 | CUUCCAGU  | CUGAUGA | X   | GAA | ACCUGAUU | AAUCAGGUA ACUGGAAG |
|    | 6308 | CUGAGUUU  | CUGAUGA | X   | GAA | ACCUCCUU | AAGGAGGUU AAACUCAG |
| 15 | 6309 | UCUGAGUU  | CUGAUGA | X   | GAA | AACCUCCU | AGGAGGUUA AACUCAGA |
|    | 6314 | บบบบบบ    | CUGAUGA | X   | GAA | AGUUUAAC | GUUAAACUC AGAAAAA  |
|    | 6331 | AAUUGACU  | CUGAUGA | x   | GAA | AGGUCUUC | GAAGACCUC AGUCAAUU |
|    | 6335 | AGAGAAUU  | CUGAUGA | X   | GAA | ACUGAGGU | ACCUCAGUC AAUUCUCU |
|    | 6339 | AAGUAGAG  | CUGAUGA | X   | GAA | AUUGACUG | CAGUCAAUU CUCUACUU |
| 20 | 6340 | AAAGUAGA  | CUGAUGA | X   | GAA | AAUUGACU | AGUCAAUUC UCUACUUU |
|    | 6342 | AAAAAGUA  | CUGAUGA | X   | GAA | AGAAUUGA | UCAAUUCUC UACUUUUU |
|    | 6344 | AAAAAAAG  | CUGAUGA | X   | GAA | AGAGAAUU | AAUUCUCUA CUUUUUUU |
|    | 6347 | AAAAAAA   | CUGAUGA | X   | GAA | AGUAGAGA | UCUCUACUU UUUUUUU  |
|    | 6348 | AAAAAAA   | CUGAUGA | X   | GAA | AAGUAGAG | CUCUACUUU UUUUUUU  |
| 25 | 6349 | AAAAAAA   | CUGAUGA | X   | GAA | AAAGUAGA | UCUACUUUU UUUUUUUU |
|    | 6350 | AAAAAAA   | CUGAUGA | X   | GAA | AAAAGUAG | CUACUUUUU UUUUUUU  |
|    | 6351 | AAAAAAA   | CUGAUGA | X   | GAA | aaaaagua | UACUUUUUU UUUUUUUU |
|    | 6352 | ааааааа   | CUGAUGA | X   | GAA | AAAAAAGU | ACUUUUUUU UUUUUUUU |
|    | 6353 | AAAAAAA   | CUGAUGA | X   | GAA | AAAAAAAG | כטטטטטטט טטטטטטט   |
| 30 | 6354 | GAAAAAA   | CUGAUGA | X   | GAA | АААААА   | טטטטטטטט טטטטטטטכ  |
|    | 6355 | GGAAAAAA  | CUGAUGA | X   | GAA | ААААААА  | מממממממ ממממממככ   |
|    | 6356 | UGGAAAAA  | CUGAUGA | X   | GAA | ААААААА  | UUUUUUUU UUUUUCCA  |
|    | 6357 | UUGGAAAA  | CUGAUGA | X   | GAA | ААААААА  | UUUUUUUU UUUUCCAA  |

|    | 6358 | UUUGGAA  | A CUGAUG  | A :        | K GA  | AAAAAAA P | UUUUUUUU UUUCCAAA  |
|----|------|----------|-----------|------------|-------|-----------|--------------------|
|    | 6359 | AUUUGGA  | A CUGAUG  | A 2        | ( GA) | AAAAAAA   | UUUUUUUU UUCCAAAU  |
|    | 6360 | GAUUUGG  | A CUGAUGI | A )        | GA,   | AAAAAAA   | UUUUUUUU UCCAAAUC  |
|    | 6361 | UGAUUUG  | G CUGAUGI | <b>A</b> 3 | GA2   | AAAAAAA   | UUUUUUUU CCAAAUCA  |
| 5  | 6362 | CUGAUUU  | CUGAUG    | <b>\</b> } | GAZ   | AAAAAAA   | UUUUUUUUC CAAAUCAG |
|    | 6368 | UAUUAUCI | J CUGAUG  | <b>X</b> X | GAA   | AUUUGGAA  | UUCCAAAUC AGAUAAUA |
|    | 6373 | UGGGCUAU | J CUGAUGA | K A        | GAA   | AUCUGAUU  | AAUCAGAUA AUAGCCCA |
|    | 6376 | UGCUGGG  | CUGAUGA   | X          | GAA   | AUUAUCUG  | CAGAUAAUA GCCCAGCA |
|    | 6388 | GUUAUCAC | CUGAUGA   | X          | GAA   | AUUUGCUG  | CAGCAAAUA GUGAUAAC |
| 10 | 6394 | UUAUUUGU | CUGAUGA   | ×          | GAA   | AUCACUAU  | AUAGUGAUA ACAAAUAA |
|    | 6401 | UAAGGUUU | CUGAUGA   | X          | GAA   | AUUUGUUA  | UAACAAAUA AAACCUUA |
|    | 6408 | GAACAGCU | CUGAUGA   | X          | GAA   | AGGUUUUA  | UAAAACCUU AGCUGUUC |
|    | 6409 | UGAACAGO | CUGAUGA   | x          | GAA   | AAGGUUUU  | AAAACCUUA GCUGUUCA |
|    | 6415 | AAGACAUG | CUGAUGA   | X          | GAA   | ACAGCUAA  | UUAGCUGUU CAUGUCUU |
| 15 | 6416 | CAAGACAU | CUGAUGA   | x          | GAA   | AACAGCUA  | UAGCUGUUC AUGUCUUG |
|    | 6421 | GAAAUCAA | CUGAUGA   | x          | GAA   | ACAUGAAC  | GUUCAUGUC UUGAUUUC |
|    | 6423 | UUGAAAUC | CUGAUGA   | x          | GAA   | AGACAUGA  | UCAUGUCUU GAUUUCAA |
|    | 6427 | AUUAUUGA | CUGAUGA   | x          | GAA   | AUCAAGAC  | GUCUUGAUU UCAAUAAU |
|    | 6428 | AAUUAUUG | CUGAUGA   | x          | GAA   | AAUCAAGA  | UCUUGAUUU CAAUAAUU |
| 20 | 6429 | UAAUUAUU | CUGAUGA   | X          | GAA   | AAAUCAAG  | CUUGAUUUC AAUAAUUA |
|    | 6433 | GAAUUAAU | CUGAUGA   | X          | GAA   | AUUGAAAU  | AUUUCAAUA AUUAAUUC |
|    | 6436 | UAAGAAUU | CUGAUGA   | x          | GAA   | AUUAUUGA  | UCAAUAAUU AAUUCUUA |
|    | 6437 | UUAAGAAU | CUGAUGA   | X          | GAA   | AAUUAUUG  | CAAUAAUUA AUUCUUAA |
|    | 6440 | UGAUUAAG | CUGAUGA   | x          | GAA   | AUUAAUUA  | UAAUUAAUU CUUAAUCA |
| 25 | 6441 | AUGAUUAA | CUGAUGA   | x          | GAA   | UUAAUUAA  | AAUUAAUUC UUAAUCAU |
|    | 6443 | UAAUGAUU | CUGAUGA   | X          | GAA   | AGAAUUAA  | UUAAUUCUU AAUCAUUA |
|    | 6444 | UUAAUGAU | CUGAUGA   | X          | GAA   | AAGAAUUA  | UAAUUCUUA AUCAUUAA |
|    | 6447 | CUCUUAAU | CUGAUGA   | X          | GAA   | AUUAAGAA  | UUCUUAAUC AUUAAGAG |
|    | 6450 | GGUCUCUU | CUGAUGA   | X          | GAA   | AUGAUUAA  | UUAAUCAUU AAGAGACC |
| 30 | 6451 | UGGUCUCU | CUGAUGA   | X          | GAA   | AAUGAUUA  | UAAUCAUUA AGAGACCA |
|    | 6461 | GUAUUUAU | CUGAUGA   | X          | GAA   | AUGGUCUC  | GAGACCAUA AUAAAUAC |
|    | 6464 |          |           |            |       |           | ACCAUAAUA AAUACUCC |
|    | 6468 | AAAAGGAG | CUGAUGA   | X          | GAA   | AUUUAUUA  | UAAUAAAUA CUCCUUUU |

|    | 6471         | UUGAAAAG | CUGAUGA | Х          | GAA | AGUAUUUA | UAAAUACUC CUUUUCAA |
|----|--------------|----------|---------|------------|-----|----------|--------------------|
|    | 6474         | CUCUUGAA | CUGAUGA | Х          | GAA | AGGAGUAU | AUACUCCUU UUCAAGAG |
|    | 6475         | UCUCUUGA | CUGAUGA | X          | GAA | AAGGAGUA | UACUCCUUU UCAAGAGA |
|    | 6476         | UUCUCUUG | CUGAUGA | X          | GAA | AAAGGAGU | ACUCCUUUU CAAGAGAA |
| 5  | 6477         | ບບບດວນບ  | CUGAUGA | . x        | GAA | AAAAGGAG | CUCCUUUUC AAGAGAAA |
|    | 6497         | ACAAUUCU | CUGAUGA | . <b>x</b> | GAA | AUGGUUUU | AAAACCAUU AGAAUUGU |
|    | 6498         | AACAAUUC | CUGAUGA | X          | GAA | AAUGGUUU | AAACCAUUA GAAUUGUU |
|    | 6503         | UGAGUAAC | CUGAUGA | X          | GAA | AUUCUAAU | AUUAGAAUU GUUACUCA |
|    | 6506         | AGCUGAGU | CUGAUGA | X          | GAA | ACAAUUCU | AGAAUUGUU ACUCAGCU |
| 10 | 6507         | GAGCUGAG | CUGAUGA | X          | GAA | AACAAUUC | GAAUUGUUA CUCAGCUC |
|    | 6510         | AAGGAGCU | CUGAUGA | X          | GAA | AGUAACAA | UUGUUACUC AGCUCCUU |
|    | 6515         | GUUUGAAG | CUGAUGA | x          | GAA | AGCUGAGU | ACUCAGCUC CUUCAAAC |
|    | 6518         | UGAGUUUG | CUGAUGA | X          | GAA | AGGAGCUG | CAGCUCCUU CAAACUCA |
|    | 6519         | CUGAGUUU | CUGAUGA | x          | GAA | AAGGAGCU | AGCUCCUUC AAACUCAG |
| 15 | 6525         | ACAAACCU | CUGAUGA | X          | GAA | AGUUUGAA | UUCAAACUC AGGUUUGU |
|    | 6530         | AUGCUACA | CUGAUGA | X          | GAA | ACCUGAGU | ACUCAGGUU UGUAGCAU |
|    | 6531         | UAUGCUAC | CUGAUGA | X          | GAA | AACCUGAG | CUCAGGUUU GUAGCAUA |
|    | 6534         | AUGUAUGC | CUGAUGA | X          | GAA | ACAAACCU | AGGUUUGUA GCAUACAU |
|    | 6539         | GACUCAUG | CUGAUGA | X          | GAA | AUGCUACA | UGUAGCAUA CAUGAGUC |
| 20 | 6547         | GAUGGAUG | CUGAUGA | x          | GAA | ACUCAUGU | ACAUGAGUC CAUCCAUC |
|    | 6551         | GACUGAUG | CUGAUGA | x          | GAA | AUGGACUC | GAGUCCAUC CAUCAGUC |
|    | <b>65</b> 55 | CUUUGACU | CUGAUGA | x          | GAA | AUGGAUGG | CCAUCCAUC AGUCAAAG |
|    | <b>65</b> 59 | CAUUCUUU | CUGAUGA | X          | GAA | ACUGAUGG | CCAUCAGUC AAAGAAUG |
|    | 6570         | CCAGAUGG | CUGAUGA | X          | GAA | ACCAUUCU | AGAAUGGUU CCAUCUGG |
| 25 | 6571         | UCCAGAUG | CUGAUGA | X          | GAA | AACCAUUC | GAAUGGUUC CAUCUGGA |
|    | 6575         | AGACUCCA | CUGAUGA | X          | GAA | AUGGAACC | GGUUCCAUC UGGAGUCU |
|    | 6582         | UACAUUAA | CUGAUGA | X          | GAA | ACUCCAGA | UCUGGAGUC UUAAUGUA |
|    | 6584         | UCUACAUU | CUGAUGA | X          | GAA | AGACUCCA | UGGAGUCUU AAUGUAGA |
|    | 6585         |          |         |            |     | AAGACUCC | GGAGUCUUA AUGUAGAA |
| 30 | 6590         | טטטכטטטכ | CUGAUGA | X          | GAA | ACAUUAAG | CUUAAUGUA GAAAGAAA |
|    | 6609         |          |         |            |     | AGUCUCCA | UGGAGACUU GUAAUAAU |
|    | 6612         |          |         |            |     | ACAAGUCU | AGACUUGUA AUAAUGAG |
|    | 6615         | UAGCUCAU | CUGAUGA | x          | GAA | AUUACAAG | CUUGUAAUA AUGAGCUA |

|    | 6623            | UUUGUAAC CUGAUGA X GAA AGCUCAUU   |                    |
|----|-----------------|-----------------------------------|--------------------|
|    | 6626            |                                   | AAUGAGCUA GUUACAAA |
|    | 6627            |                                   | ACAMAGUG           |
|    | 6637            | THIS COURT A GAA AACUAGCU         |                    |
| 5  |                 | STORES COURT A GAM AGCACUUU       | GUUCAUUA           |
| 3  |                 | TOURS COUNTRY AND ACARGUAC        | CAUUMMAA           |
|    | 6641            | STOREST COGAGGA & GAA AACAAGCA    | TOUGOUS MUUMAMAU   |
|    | 6644            | TOTAL COURT A GAA AUGAACAA        | TO TOUR OAGE       |
|    | 6645            | TOTAL COGNOR & GAM MAUGAACA       | UGUUCAUUA AAAUAGCA |
|    | 6650            | TOWNSON COUNTRY OF A GAM AUUUUAAU | AUUAAAAUA GCACUGAA |
| 10 |                 | CAUGUUUC CUGAUGA X GAA AUUUUCAG   | CUGAAAAUU GAAACAUG |
|    | 6674            | TOURS OF THE SAM AUUCAUGU         | ACAUGAAUU AACUGAUA |
|    | 6675            | UUAUCAGU CUGAUGA X GAA AAUUCAUG   | CAUGAAUUA ACUGAUAA |
|    | 6682            | UGGAAUAU CUGAUGA X GAA AUCAGUUA   | UAACUGAUA AUAUUCCA |
|    |                 | GAUUGGAA CUGAUGA X GAA AUUAUCAG   | CUGAUAAUA UUCCAAUC |
| 15 | 6687            | AUGAUUGG CUGAUGA X GAA AUAUUAUC   | GAUAAUAUU CCAAUCAU |
|    | 6688            | AAUGAUUG CUGAUGA X GAA AAUAUUAU   | AUAAUAUUC CAAUCAUU |
|    | 6693            | UGGCAAAU CUGAUGA X GAA AUUGGAAU   | AUUCCAAUC AUUUGCCA |
|    | 6696            | AAAUGGCA CUGAUGA X GAA AUGAUUGG   | CCAAUCAUU UGCCAUUU |
|    |                 | UAAAUGGC CUGAUGA X GAA AAUGAUUG   | CAAUCAUUU GCCAUUUA |
| 20 |                 | UUGUCAUA CUGAUGA X GAA AUGGCAAA   | UUUGCCAUU UAUGACAA |
|    | 6704            | UUUGUCAU CUGAUGA X GAA AAUGGCAA   | UUGCCAUUU AUGACAAA |
|    | 6705            | UUUUGUCA CUGAUGA X GAA AAAUGGCA   | UGCCAUUUA UGACAAAA |
|    | 6719            | UUAGUGCC CUGAUGA X GAA ACCAUUUU   | AAAAUGGUU GGCACUAA |
|    | 6726            | UUCUUUGU CUGAUGA X GAA AGUGCCAA   | UUGGCACUA ACAAAGAA |
| 25 | 6743            | CUGAAAGG CUGAUGA X GAA AGUGCUCG   | CGAGCACUU CCUUUCAG |
|    | 6744 1          | UCUGAAAG CUGAUGA X GAA AAGUGCUC   | GAGCACUUC CUUUCAGA |
|    | 6747            | AACUCUGA CUGAUGA X GAA AGGAAGUG   | CACUUCCUU UCAGAGUU |
|    | 6748            | AAACUCUG CUGAUGA X GAA AAGGAAGU   | ACUUCCUUU CAGAGUUU |
|    | 6749 (          | GAAACUCU CUGAUGA X GAA AAAGGAAG   | CUUCCUUUC AGAGUUUC |
| 30 | 6755 7          | AUCUCAGA CUGAUGA X GAA ACUCUGAA   | UUCAGAGUU UCUGAGAU |
|    | 6756 t          | JAUCUCAG CUGAUGA X GAA AACUCUGA   | UCAGAGUUU CUGAGAUA |
|    | 6 <b>7</b> 57 t | JUAUCUCA CUGAUGA X GAA AAACUCUG   | CAGAGUUUC UGAGAUAA |
|    | 6764 7          | ACGUACAU CUGAUGA X GAA AUCUCAGA   | UCUGAGAUA AUGUACGU |
|    |                 |                                   |                    |

|    | 6760         | Ø17100100  | <i>a</i> |   |     |          |  |
|----|--------------|------------|----------|---|-----|----------|--|
|    | 6769         |            |          |   |     | ACAUUAUC | ordered to the contract of the |
|    | 6781         |            |          |   |     | ACUGUUCC | GGAACAGUC UGGGUGGA   |
|    | 6814         |            |          |   |     | ACUUGCAC | GUGCAAGUC UGUGUCUU   |
|    | 6820         | ACUGACAA   | CUGAUGA  | X | GAA | ACACAGAC | GUCUGUGUC UUGUCAGU   |
| 5  | 6822         | GGACUGAC   | CUGAUGA  | X | GAA | AGACACAG | CUGUGUCUU GUCAGUCC   |
|    | 6825         | CUUGGACU   | CUGAUGA  | X | GAA | ACAAGACA | UGUCUUGUC AGUCCAAG   |
|    | 6829         | ACUUCUUG   | CUGAUGA  | X | GAA | ACUGACAA | UUGUCAGUC CAAGAAGU   |
|    | 6851         | CUAAAAUU   | CUGAUGA  | X | GAA | ACAUCUCG | CGAGAUGUU AAUUUUAG   |
|    | 6852         | CCUAAAAU   | CUGAUGA  | X | GAA | AACAUCUC | GAGAUGUUA AUUUUAGG   |
| 10 | 6855         | GUCCCUAA   | CUGAUGA  | X | GAA | AUUAACAU | AUGUUAAUU UUAGGGAC   |
|    | 6856         | GGUCCCUA   | CUGAUGA  | X | GAA | AAUUAACA | UGUUAAUUU UAGGGACC   |
|    | 6857         | GGGUCCCU   | CUGAUGA  | x | GAA | AAAUUAAC | GUUAAUUUU AGGGACCC   |
|    | 6858         | CGGGUCCC   | CUGAUGA  | x | GAA | AAAAUUAA | UUAAUUUUA GGGACCCG   |
|    | 6872         | UAGGAAAC   | CUGAUGA  | x | GAA | AGGCACGG | CCGUGCCUU GUUUCCUA   |
| 15 | 6875         | GGCUAGGA   | CUGAUGA  | x | GAA | ACAAGGCA | UGCCUUGUU UCCUAGCC   |
|    | <b>687</b> 6 | GGGCUAGG   | CUGAUGA  | x | GAA | AACAAGGC | GCCUUGUUU CCUAGCCC   |
|    | 6877         | UGGGCUAG   | CUGAUGA  | x | GAA | AAACAAGG | CCUUGUUUC CUAGCCCA   |
|    | 6880         | UUGUGGGC ( | CUGAUGA  | x | GAA | AGGAAACA | UGUUUCCUA GCCCACAA   |
|    | 6901         | AUCUGUUU ( | CUGAUGA  | X | GAA | AUGUUUGC | GCAAACAUC AAACAGAU   |
| 20 | 6910         | CUAGCGAG   | CUGAUGA  | X | GAA | AUCUGUUU | AAACAGAUA CUCGCUAG   |
|    | 6913         | AGGCUAGC ( | CUGAUGA  | X | GAA | AGUAUCUG | CAGAUACUC GCUAGCCU   |
|    | 6917         | AAUGAGGC ( | CUGAUGA  | x | GAA | AGCGAGUA | UACUCGCUA GCCUCAUU   |
|    | 6922         | AUUUAAAU ( | CUGAUGA  | x | GAA | AGGCUAGC | GCUAGCCUC AUUUAAAU   |
|    | 6925         | UCAAUUUA ( | CUGAUGA  | x | GAA | AUGAGGCU | AGCCUCAUU UAAAUUGA   |
| 25 | 6926         | AUCAAUUU ( | CUGAUGA  | x | GAA | AAUGAGGC | GCCUCAUUU AAAUUGAU   |
|    | 6927         | AAUCAAUU ( | CUGAUGA  | x | GAA | AAAUGAGG | CCUCAUUUA AAUUGAUU   |
|    | 6931         | CUUUAAUC ( | CUGAUGA  | X | GAA | UAAAUUUA | AUUUAAAUU GAUUAAAG   |
|    | 6935         | ccuccuuu d | TUGAUGA  | X | GAA | AUCAAUUU | AAAUUGAUU AAAGGAGG   |
|    | 6936         | מכמככת מ   | CUGAUGA  | X | GAA | AAUCAAUU | AAUUGAUUA AAGGAGGA   |
| 30 | 6951         | CGGCCAAA C | CUGAUGA  | X | GAA | AUGCACUC | GAGUGCAUC UUUGGCCG   |
|    | 6953         | GUCGGCCA C | CUGAUGA  | X | GAA | AGAUGCAC | GUGCAUCUU UGGCCGAC   |
|    | 6954         | UGUCGGCC C | CUGAUGA  | X | GAA | AAGAUGCA | UGCAUCUUU GGCCGACA   |
|    | 6970         | CACACAGU C | TUGAUGA  | X | GAA | ACACCACU | AGUGGUGUA ACUGUGUG   |

|    | 7026 | AACACAC  | A CUGAUG  | A 2        | ( GA) | A ACACCCAC | GUGGGUGUA UGUGUGUU |
|----|------|----------|-----------|------------|-------|------------|--------------------|
|    | 7034 | AUGCACA  | A CUGAUG! | <b>C</b> A | ( GA) | A ACACACAU | AUGUGUGUU UUGUGCAU |
|    | 7035 | UAUGCAC  | A CUGAUGA | A 3        | ( GAZ | AACACACA   | UGUGUGUUU UGUGCAUA |
|    | 7036 | UUAUGCA  | CUGAUGA   | X X        | GA    | AAACACAC   | GUGUGUUUU GUGCAUAA |
| 5  | 7043 | UAAAUAGU | J CUGAUGA | K          | GA.   | AUGCACAA   | UUGUGCAUA ACUAUUUA |
|    | 7047 | UCCUUAA  | CUGAUGA   | K A        | GAA   | AGUUAUGC   | GCAUAACUA UUUAAGGA |
|    | 7049 | UUUCCUU  | CUGAUGA   | X          | GAA   | AUAGUUAU   | AUAACUAUU UAAGGAAA |
|    | 7050 | GUUUCCUU | CUGAUGA   | X          | GAA   | AAUAGUUA   | UAACUAUUU AAGGAAAC |
|    | 7051 | AGUUUCCU | CUGAUGA   | X          | GAA   | AAAUAGUU   | AACUAUUUA AGGAAACU |
| 10 | 7065 | AACUUUAA | CUGAUGA   | X          | GAA   | AUUCCAGU   | ACUGGAAUU UUAAAGUU |
|    | 7066 | UAACUUUA | CUGAUGA   | X          | GAA   | AAUUCCAG   | CUGGAAUUU UAAAGUUA |
|    | 7067 | GUAACUUU | CUGAUGA   | X          | GAA   | AAAUUCCA   | UGGAAUUUU AAAGUUAC |
|    | 7068 | AGUAACUU | CUGAUGA   | x          | GAA   | AAAAUUCC   | GGAAUUUUA AAGUUACU |
|    | 7073 | AUAAAAGU | CUGAUGA   | X          | GAA   | ACUUUAAA   | UUUAAAGUU ACUUUUAU |
| 15 | 7074 | UAUAAAAG | CUGAUGA   | X          | GAA   | AACUUUAA   | UUAAAGUUA CUUUUAUA |
|    | 7077 | UUGUAUAA | CUGAUGA   | X          | GAA   | AGUAACUU   | AAGUUACUU UUAUACAA |
|    | 7078 | UUUGUAUA | CUGAUGA   | x          | GAA   | AAGUAACU   | AGUUACUUU UAUACAAA |
|    | 7079 | GUUUGUAU | CUGAUGA   | x          | GAA   | AAAGUAAC   | GUUACUUUU AUACAAAC |
|    | 7080 | GGUUUGUA | CUGAUGA   | x          | GAA   | Aaaaguaa   | UUACUUUUA UACAAACC |
| 20 | 7082 | UUGGUUUG | CUGAUGA   | x          | GAA   | AUAAAAGU   | ACUUUUAUA CAAACCAA |
|    | 7095 | GUAGCAUA | CUGAUGA   | x          | GAA   | AUUCUUGG   | CCAAGAAUA UAUGCUAC |
|    | 7097 | CUGUAGCA | CUGAUGA   | x          | GAA   | AUAUUCUU   | AAGAAUAUA UGCUACAG |
|    | 7102 | UAUAUCUG | CUGAUGA   | x          | GAA   | AGCAUAUA   | UAUAUGCUA CAGAUAUA |
|    | 7108 | CUGUCUUA | CUGAUGA   | X          | GAA   | AUCUGUAG   | CUACAGAUA UAAGACAG |
| 25 | 7110 | GUCUGUCU | CUGAUGA   | x          | GAA   | AUAUCUGU   | ACAGAUAUA AGACAGAC |
|    | 7124 | UAGGACCA | CUGAUGA   | x          | GAA   | ACCAUGUC   | GACAUGGUU UGGUCCUA |
|    | 7125 | AUAGGACC | CUGAUGA   | x          | GAA   | AACCAUGU   | ACAUGGUUU GGUCCUAU |
|    | 7129 | AAAUAUAG | CUGAUGA   | x          | GAA   | ACCAAACC   | GGUUUGGUC CUAUAUUU |
|    | 7132 | UAGAAAUA | CUGAUGA   | x          | GAA   | AGGACCAA   | UUGGUCCUA UAUUUCUA |
| 30 | 7134 | ACUAGAAA | CUGAUGA   | x          | GAA   | AUAGGACC   | GGUCCUAUA UUUCUAGU |
|    | 7136 | UGACUAGA | CUGAUGA   | x          | GAA   | AUAUAGGA   | UCCUAUAUU UCUAGUCA |
|    | 7137 | AUGACUAG | CUGAUGA   | x          | GAA   | AAUAUAGG   | CCUAUAUUU CUAGUCAU |
|    | 7138 | CAUGACUA | CUGAUGA   | x          | GAA   | AAAUAUAG   | CUAUAUUUC UAGUCAUG |
|    |      |          |           |            |       |            |                    |

|     | 7140 | AUCAUGAC   | CUGAUGA | X | GAA | AGAAAUAU  | AUAUUUCU  | A GUCAUGAU |
|-----|------|------------|---------|---|-----|-----------|-----------|------------|
|     | 7143 | UUCAUCAU   | CUGAUGA | X | GAA | ACUAGAAA  | UUUCUAGU  | AUGAUGAA   |
|     | 7155 | AUACAAAA   | CUGAUGA | X | GAA | ACAUUCAU  | AUGAAUGU? | UUUUGUAU   |
|     | 7157 | GUAUACAA   | CUGAUGA | X | GAA | AUACAUUC  | GAAUGUAU  | UUGUAUAC   |
| - 5 | 7158 | GGUAUACA   | CUGAUGA | X | GAA | AAUACAUU  | AAUGUAUU  | J UGUAUACC |
|     | 7159 | UGGUAUAC   | CUGAUGA | X | GAA | AAAUACAU  | AUGUAUUUT | GUAUACCA   |
|     | 7162 | AGAUGGUA   | CUGAUGA | X | GAA | ACAAAAUA  | UAUUUUGUA | UACCAUCU   |
|     | 7164 | GAAGAUGG   | CUGAUGA | X | GAA | AUACAAAA  | UUUUGUAUA | CCAUCUUC   |
|     | 7169 | UAUAUGAA   | CUGAUGA | X | GAA | AUGGUAUA  | UAUACCAUC | UUCAUAUA   |
| 10  | 7171 | AUUAUAUG ( | CUGAUGA | X | GAA | AGAUGGUA  | UACCAUCUU | CAUAUAAU   |
|     | 7172 | UAUUAUAU ( | CUGAUGA | X | GAA | AAGAUGGU  | ACCAUCUUC | AUAUAAUA   |
|     | 7175 | GUAUAUUA ( | CUGAUGA | X | GAA | AUGAAGAU  | AUCUUCAUA | UAAUAUAC   |
|     | 7177 | AAGUAUAU ( | CUGAUGA | x | GAA | AUAUGAAG  | CUUCAUAUA | AUAUACUU   |
|     | 7180 | UUUAAGUA ( | CUGAUGA | X | GAA | AUUAUAUG  | CAUAUAAUA | UACUUAAA   |
| 15  | 7182 | UUUUUAAG ( | CUGAUGA | X | GAA | AUAUUAUA  | UAUAAUAUA | CUUAAAAA   |
|     | 7185 | AUAUUUUU C | CUGAUGA | X | GAA | AGUAUAUU  | AAUAUACUU | DADAAAAA   |
|     | 7186 | AAUAUUUU C | CUGAUGA | X | GAA | AAGUAUAU  | AUAUACUUA | AAAAUAUU   |
|     | 7192 | UUAAGAAA C | TUGAUGA | x | GAA | AAUUUUUA  | UUAAAAAUA | UUUCUUAA   |
|     | 7194 | AAUUAAGA C | UGAUGA  | X | GAA | UUUUUUAUA | AAAAAUAUU | UCUUAAUU   |
| 20  | 7195 | CAAUUAAG C | UGAUGA  | X | GAA | UUUUAUAA  | AAAAUAUUU | CUUAAUUG   |
|     | 7196 | CCAAUUAA C | UGAUGA  | X | GAA | UUUAUAAA  | AAAUAUUUC | UUAAUUGG   |
|     | 7198 | UCCCAAUU C | UGAUGA  | X | GAA | AGAAAUAU  | AUAUUUCUU | AAUUGGGA   |
|     | 7199 | AUCCCAAU C | UGAUGA  | X | GAA | AAGAAAUA  | UAUUUCUUA | AUUGGGAU   |
|     | 7202 | CAAAUCCC C | UGAUGA  | X | GAA | AUUAAGAA  | UUCUUAAUU | GGGAUUUG   |
| 25  | 7208 | CGAUUACA C | UGAUGA  | X | GAA | AUCCCAAU  | AUUGGGAUU | UGUAAUCG   |
|     | 7209 | ACGAUUAC C | UGAUGA  | X | GAA | AAUCCCAA  | UUGGGAUUU | GUAAUCGU   |
|     | 7212 | GGUACGAU C | UGAUGA  | X | GAA | ACAAAUCC  | GGAUUUGUA | AUCGUACC   |
|     | 7215 | GUUGGUAC C | UGAUGA  | X | GAA | AUUACAAA  | UUUGUAAUC | GUACCAAC   |
|     | 7218 | UAAGUUGG C | UGAUGA  | X | GAA | ACGAUUAC  | GUAAUCGUA | CCAACUUA   |
| 30  | 7225 | UAUCAAUU C | UGAUGA  | X | GAA | AGUUGGUA  | UACCAACUU | AAUUGAUA   |
|     | 7226 | UUAUCAAU C | UGAUGA  | X | GAA | AAGUUGGU  | ACCAACUUA | AUUGAUAA   |
|     | 7229 | AGUUUAUC C | UGAUGA  | X | GAA | AUUAAGUU  | AACUUAAUU | GAUAAACU   |
|     | 7233 | GCCAAGUU C | UGAUGA  | X | GAA | AUCAAUUA  | UAAUUGAUA | AACUUGGC   |

|    | 7238 | CAGUUGCC | CUGAUGA | X | GAA | AGUUUAUC  | GAUAAACUU GGCAACUG |
|----|------|----------|---------|---|-----|-----------|--------------------|
|    | 7249 | GAACAUAA | CUGAUGA | X | GAA | AGCAGUUG  | CAACUGCUU UUAUGUUC |
|    | 7250 | AGAACAUA | CUGAUGA | X | GAA | AAGCAGUU  | AACUGCUUU UAUGUUCU |
|    | 7251 | CAGAACAU | CUGAUGA | X | GAA | AAAGCAGU  | ACUGCUUUU AUGUUCUG |
| 5  | 7252 | ACAGAACA | CUGAUGA | X | GAA | AAAAGCAG  | CUGCUUUUA UGUUCUGU |
|    | 7256 | GGAGACAG | CUGAUGA | X | GAA | ACAUAAAA  | UUUUAUGUU CUGUCUCC |
|    | 7257 | AGGAGACA | CUGAUGA | X | GAA | AACAUAAA  | UUUAUGUUC UGUCUCCU |
|    | 7261 | UGGAAGGA | CUGAUGA | X | GAA | ACAGAACA  | UGUUCUGUC UCCUUCCA |
|    | 7263 | UAUGGAAG | CUGAUGA | X | GAA | AGACAGAA  | UUCUGUCUC CUUCCAUA |
| 10 | 7266 | AUUUAUGG | CUGAUGA | x | GAA | AGGAGACA  | UGUCUCCUU CCAUAAAU |
|    | 7267 | AAUUUAUG | CUGAUGA | X | GAA | AAGGAGAC  | GUCUCCUUC CAUAAAUU |
|    | 7271 | GAAAAAUU | CUGAUGA | X | GAA | AUGGAAGG  | CCUUCCAUA AAUUUUUC |
|    | 7275 | UUUUGAAA | CUGAUGA | x | GAA | AUUUAUGG  | CCAUAAAUU UUUCAAAA |
|    | 7276 | AUUUUGAA | CUGAUGA | X | GAA | AAUUUAUG  | CAUAAAUUU UUCAAAAU |
| 15 | 7277 | UAUUUUGA | CUGAUGA | X | GAA | DADUUDAAA | AUAAAUUUU UCAAAAUA |
|    | 7278 | GUAUUUUG | CUGAUGA | X | GAA | AUUUAAAA  | UAAAUUUUU CAAAAUAC |
|    | 7279 | AGUAUUUU | CUGAUGA | x | GAA | UUUAAAAA  | AAAUUUUUC AAAAUACU |
|    | 7285 | UGAAUUAG | CUGAUGA | X | GAA | AUUUUGAA  | UUCAAAAUA CUAAUUCA |
|    | 7288 | UGUUGAAU | CUGAUGA | X | GAA | AGUAUUUU  | AAAAUACUA AUUCAACA |
| 20 | 7291 | CUUUGUUG | CUGAUGA | X | GAA | AUUAGUAU  | AUACUAAUU CAACAAAG |
|    | 7292 | ncnngan  | CUGAUGA | X | GAA | AAUUAGUA  | UACUAAUUC AACAAAGA |
|    | 7308 | ААААААА  | CUGAUGA | X | GAA | AGCUUUUU  | AAAAAGCUC UUUUUUU  |
|    | 7310 | GGAAAAAA | CUGAUGA | X | GAA | AGAGCUUU  | AAAGCUCUU UUUUUUCC |
|    | 7311 | AGGAAAAA | CUGAUGA | x | GAA | AAGAGCUU  | AAGCUCUUU UUUUUCCU |
| 25 | 7312 | UAGGAAAA | CUGAUGA | x | GAA | AAAGAGCU  | AGCUCUUUU UUUUCCUA |
|    | 7313 | UUAGGAAA | CUGAUGA | X | GAA | AAAAGAGC  | GCUCUUUUU UUUCCUAA |
|    | 7314 | UUUAGGAA | CUGAUGA | x | GAA | AAAAAGAG  | CUCUUUUUU UUCCUAAA |
|    | 7315 | UUUUAGGA | CUGAUGA | X | GAA | AAAAAAGA  | UCUUUUUUU UCCUAAAA |
|    | 7316 | AUUUUAGG | CUGAUGA | X | GAA | AAAAAAAG  | CUUUUUUU CCUAAAAU  |
| 30 | 7317 | UAUUUUAG | CUGAUGA | X | GAA | AAAAAAA   | UUUUUUUC CUAAAAUA  |
|    | 7320 | GUUUAUUU | CUGAUGA | x | GAA | AGGAAAA   | UUUUUCCUA AAAUAAAC |
|    | 7325 | UUUGAGUU | CUGAUGA | x | GAA | AUUUUAGG  | CCUAAAAUA AACUCAAA |
|    | 7330 | AUAAAUUU | CUGAUGA | x | GAA | AGUUUAUU  | AAUAAACUC AAAUUUAU |

|    | 7335         | CAAGGAUA | CUGAUGA | X | GAA | AUUUGAGU | ACUCAAAUU | UAUCCUUG |
|----|--------------|----------|---------|---|-----|----------|-----------|----------|
|    | 7336         | ACAAGGAU | CUGAUGA | × | GAA | AAUUUGAG | CUCAAAUUU | AUCCUUGU |
|    | 7337         | AACAAGGA | CUGAUGA | × | GAA | AAAUUUGA | UCAAAUUUA | nccnnenn |
|    | 7339         | UAAACAAG | CUGAUGA | X | GAA | UUUAAAUA | AAAUUUAUC | CUUGUUUA |
| 5  | 7342         | CUCUAAAC | CUGAUGA | x | GAA | AGGAUAAA | UUUAUCCUU | GUUUAGAG |
|    | 7345         | CUGCUCUA | CUGAUGA | x | GAA | ACAAGGAU | AUCCUUGUU | UAGAGCAG |
|    | 7346.        | UCUGCUCU | CUGAUGA | x | GAA | AACAAGGA | uccuuguuu | AGAGCAGA |
|    | 7347         | CUCUGCUC | CUGAUGA | X | GAA | AAACAAGG | CCUUGUUUA | GAGCAGAG |
|    | 7362         | ບບບບບດ   | CUGAUGA | x | GAA | AUUUUUCU | AGAAAAAUU | AAGAAAA  |
| 10 | 7363         | GUUUUUCU | CUGAUGA | x | GAA | AAUUUUUC | GAAAAAUUA | AGAAAAAC |
|    | 7373         | CCAUUUCA | CUGAUGA | x | GAA | AGUUUUUC | GAAAAACUU | UGAAAUGG |
|    | 7374         | ACCAUUUC | CUGAUGA | X | GAA | AAGUUUUU | AAAAACUUU | GAAAUGGU |
|    | 7383         | UUUUUUGA | CUGAUGA | X | GAA | ACCAUUUC | GAAAUGGUC | UCAAAAAA |
|    | 7385         | AAUUUUUU | CUGAUGA | x | GAA | AGACCAUU | AAUGGUCUC | DUAAAAA  |
| 15 | 7393         | UAUUUAGC | CUGAUGA | x | GAA | AUUUUUUG | CAAAAAAUU | GCUAAAUA |
|    | <b>739</b> 7 | AAAAUAUU | CUGAUGA | x | GAA | AGCAAUUU | AAAUUGCUA | AAUAUUUU |
|    | 7401         | AUUGAAAA | CUGAUGA | x | GAA | AUUUAGCA | UGCUAAAUA | UUUUCAAU |
|    | 7403         | CCAUUGAA | CUGAUGA | x | GAA | AUAUUUAG | CUAAAUAUU | UUCAAUGG |
|    | 7404         | UCCAUUGA | CUGAUGA | x | GAA | AAUAUUUA | UNDAUAGU  | UCAAUGGA |
| 20 | 7405         | UUCCAUUG | CUGAUGA | x | GAA | UUUAUAAA | UUUUAUAAA | CAAUGGAA |
|    | 7406         | UUUCCAUU | CUGAUGA | x | GAA | UUAUAAAA | AAUAUUUUC | AAUGGAAA |
|    | 7418         | CUAACAUU | CUGAUGA | x | GAA | AGUUUUCC | GGAAAACUA | AAUGUUAG |
|    | 7424         | GCUAAACU | CUGAUGA | x | GAA | ACAUUUAG | CUAAAUGUU | AGUUUAGC |
|    | 7425         | AGCUAAAC | CUGAUGA | x | GAA | AACAUUUA | UAAAUGUUA | GUUUAGCU |
| 25 | 7428         | AUCAGCUA | CUGAUGA | X | GAA | ACUAACAU | AUGUUAGUU | UAGCUGAU |
|    | 7429         | AAUCAGCU | CUGAUGA | X | GAA | AACUAACA | UGUUAGUUU | AGCUGAUU |
|    | 7430         | CAAUCAGC | CUGAUGA | X | GAA | AAACUAAC | GUUAGUUUA | GCUGAUUG |
|    | 7437         | CCCCAUAC | CUGAUGA | X | GAA | AUCAGCUA | UAGCUGAUU | GUAUGGGG |
|    | 7440         | AAACCCCA | CUGAUGA | X | GAA | ACAAUCAG | CUGAUUGUA | UGGGGUUU |
| 30 | 7447         | GGUUCGAA | CUGAUGA | X | GAA | ACCCCAUA | UAUGGGGUU | UUCGAACC |
|    | 7448         | AGGUUCGA | CUGAUGA | x | GAA | AACCCCAU | AUGGGGUUU | UCGAACCU |
|    | 7449         | AAGGUUCG | CUGAUGA | x | GAA | AAACCCCA | UGGGGUUUU | CGAACCUU |
|    | 7450         | AAAGGUUC | CUGAUGA | x | GAA | AAAACCCC | GGGGUUUUC | GAACCUUU |

|    | 7457 | AAAAGUGA | A CUGAUGA | <b>A</b> > | GAZ | A AGGUUCGA | UCGAACCUU UCACUUUU    |
|----|------|----------|-----------|------------|-----|------------|-----------------------|
|    | 7458 | AAAAAGU  | G CUGAUGA | K A        | GAA | AAGGUUCG   | CGAACCUUU CACUUUUU    |
|    | 7459 | CAAAAAGU | J CUGAUGA | X A        | GAA | AAAGGUUC   | GAACCUUUC ACUUUUUG    |
|    | 7463 | CAAACAA  | A CUGAUGA | X A        | GAA | AGUGAAAG   | CUUUCACUU UUUGUUUG    |
| 5  | 7464 | ACAAACAA | CUGAUGA   | X          | GAA | AAGUGAAA   | UUUCACUUU UUGUUUGU    |
|    | 7465 | AACAAACA | CUGAUGA   | X          | GAA | AAAGUGAA   | UUCACUUUU UGUUUGUU    |
|    | 7466 | AAACAAAC | CUGAUGA   | X          | GAA | AAAAGUGA   | UCACUUUUU GUUUGUUU    |
|    | 7469 | GUAAAACA | CUGAUGA   | X          | GAA | ACAAAAAG   | CUUUUUGUU UGUUUUAC    |
|    | 7470 | GGUAAAAC | CUGAUGA   | . <b>x</b> | GAA | AACAAAAA   | UUUUUGUUU GUUUUACC    |
| 10 | 7473 | AUAGGUAA | CUGAUGA   | X          | GAA | ACAAACAA   | UUGUUUGUU UUACCUAU    |
|    | 7474 | AAUAGGUA | CUGAUGA   | X          | GAA | AACAAACA   | UGUUUGUUU UACCUAUU    |
|    | 7475 | AAAUAGGU | CUGAUGA   | X          | GAA | AAACAAAC   | GUUUGUUUU ACCUAUUU    |
|    | 7476 | GAAAUAGG | CUGAUGA   | X          | GAA | AAAACAAA   | UUUGUUUUA CCUAUUUC    |
|    | 7480 | UUGUGAAA | CUGAUGA   | X          | GAA | AGGUAAAA   | UUUUACCUA UUUCACAA    |
| 15 | 7482 | AGUUGUGA | CUGAUGA   | X          | GAA | AUAGGUAA   | UUACCUAUU UCACAACU    |
|    | 7483 | CAGUUGUG | CUGAUGA   | x          | GAA | AAUAGGUA   | UACCUAUUU CACAACUG    |
|    | 7484 | ACAGUUGU | CUGAUGA   | X          | GAA | AAAUAGGU   | ACCUAUUUC ACAACUGU    |
|    | 7495 | UGGCAAUU | CUGAUGA   | x          | GAA | ACACAGUU   | AACUGUGUA AAUUGCCA    |
|    | 7499 | UUAUUGGC | CUGAUGA   | X          | GAA | AUUUACAC   | GUGUAAAUU GCCAAUAA    |
| 20 | 7506 | ACAGGAAU | CUGAUGA   | X          | GAA | AUUGGCAA   | UUGCCAAUA AUUCCUGU    |
|    | 7509 | UGGACAGG | CUGAUGA   | X          | GAA | AUUAUUGG   | CCAAUAAUU CCUGUCCA    |
|    | 7510 | AUGGACAG | CUGAUGA   | X          | GAA | AAUUAUUG   | CAAUAAUUC CUGUCCAU    |
|    | 7515 | UUUUCAUG | CUGAUGA   | X          | GAA | ACAGGAAU   | AUUCCUGUC CAUGAAAA    |
|    | 7531 | CACUGGAU | CUGAUGA   | X          | GAA | AUUUGCAU   | AUGCAAAUU AUCCAGUG    |
| 25 | 7532 | ACACUGGA | CUGAUGA   | X          | GAA | AAUUUGCA   | UGCAAAUUA UCCAGUGU    |
|    | 7534 | CUACACUG | CUGAUGA   | X          | GAA | AUAAUUUG   | CAAAUUAUC CAGUGUAG    |
|    | 7541 | AAUAUAUC | CUGAUGA   | X          | GAA | ACACUGGA   | UCCAGUGUA GAUAUAUU    |
|    | 7545 | GUCAAAUA | CUGAUGA   | x          | GAA | AUCUACAC   | GUGUAGAUA UAUUUGAC    |
|    | 7547 | UGGUCAAA |           |            |     |            | GUAGAUAUA UUUGACCA    |
| 30 | 7549 | GAUGGUCA | CUGAUGA   | X          | GAA | AUAUAUCU   | AGAUAUAUU UGACCAUC    |
|    | 7550 | UGAUGGUC | CUGAUGA   | x          | GAA | AAUAUAUC   | GAUAUAUUU GACCAUCA    |
|    | 7557 | CAUAGGGU | CUGAUGA   | x          | GAA | AUGGUCAA   | UUGACCAUC ACCCUAUG    |
|    | 7563 | AAUAUCCA | CUGAUGA   | x          | GAA | AGGGUGAU   | AUCACCCUA UGGALIATITI |

|    | 7569 | CUAGCCAA | CUGAUGA | X   | GAZ | AUCCAUAG | CUAUGGAUA UUGGCUAG |
|----|------|----------|---------|-----|-----|----------|--------------------|
|    | 7571 | AACUAGCO | CUGAUGA | . X | GAZ | AUAUCCAU | AUGGAUAUU GGCUAGUU |
|    | 7576 | GGCAAAAC | CUGAUGA | X   | GAA | AGCCAAUA | UAUUGGCUA GUUUUGCC |
|    | 7579 | AAAGGCAA | CUGAUGA | X   | GAA | ACUAGCCA | UGGCUAGUU UUGCCUUU |
| 5  | 7580 | UAAAGGCA | CUGAUGA | X   | GAA | AACUAGCC | GGCUAGUUU UGCCUUUA |
|    | 7581 | AUAAAGGC | CUGAUGA | X   | GAA | AAACUAGC | GCUAGUUUU GCCUUUAU |
|    | 7586 | GCUUAAUA | CUGAUGA | х   | GAA | AGGCAAAA | UUUUGCCUU UAUUAAGC |
|    | 7587 | UGCUUAAU | CUGAUGA | X   | GAA | AAGGCAAA | UUUGCCUUU AUUAAGCA |
|    | 7588 | UUGCUUAA | CUGAUGA | x   | GAA | AAAGGCAA | UUGCCUUUA UUAAGCAA |
| 10 | 7590 | AUUUGCUU | CUGAUGA | X   | GAA | AUAAAGGC | GCCUUUAUU AAGCAAAU |
| ,  | 7591 | AAUUUGCU | CUGAUGA | X   | GAA | AAUAAAGG | CCUUUAUUA AGCAAAUU |
|    | 7599 | CUGAAAUG | CUGAUGA | X   | GAA | AUUUGCUU | AAGCAAAUU CAUUUCAG |
|    | 7600 | GCUGAAAU | CUGAUGA | X   | GAA | AAUUUGCU | AGCAAAUUC AUUUCAGC |
|    | 7603 | CAGGCUGA | CUGAUGA | X   | GAA | AUGAAUUU | AAAUUCAUU UCAGCCUG |
| 15 | 7604 | UCAGGCUG | CUGAUGA | x   | GAA | AAUGAAUU | AAUUCAUUU CAGCCUGA |
|    | 7605 | UUCAGGCU | CUGAUGA | X   | GAA | AAAUGAAU | AUUCAUUUC AGCCUGAA |
|    | 7617 | UAUAGGCA | CUGAUGA | X   | GAA | ACAUUCAG | CUGAAUGUC UGCCUAUA |
|    | 7623 | AGAAUAUA | CUGAUGA | X   | GAA | AGGCAGAC | GUCUGCCUA UAUAUUCU |
|    | 7625 | AGAGAAUA | CUGAUGA | X   | GAA | AUAGGCAG | CUGCCUAUA UAUUCUCU |
| 20 | 7627 | GCAGAGAA | CUGAUGA | X   | GAA | AUAUAGGC | GCCUAUAUA UUCUCUGC |
|    | 7629 | GAGCAGAG | CUGAUGA | X   | GAA | AUAUAUAG | CUAUAUAUU CUCUGCUC |
|    | 7630 | AGAGCAGA | CUGAUGA | X   | GAA | AAUAUAUA | UAUAUAUUC UCUGCUCU |
|    | 7632 | AAAGAGCA | CUGAUGA | X   | GAA | AGAAUAUA | UAUAUUCUC UGCUCUUU |
|    | 7637 | AAUACAAA | CUGAUGA | X   | GAA | AGCAGAGA | UCUCUGCUC UUUGUAUU |
| 25 | 7639 | AGAAUACA | CUGAUGA | X   | GAA | AGAGCAGA | UCUGCUCUU UGUAUUCU |
|    | 7640 | GAGAAUAC | CUGAUGA | X   | GAA | AAGAGCAG | CUGCUCUUU GUAUUCUC |
|    | 7643 | AAGGAGAA | CUGAUGA | X   | GAA | ACAAAGAG | CUCUUUGUA UUCUCCUU |
|    | 7645 | CAAAGGAG | CUGAUGA | X   | GAA | AUACAAAG | CUUUGUAUU CUCCUUUG |
|    | 7646 | UCAAAGGA | CUGAUGA | X   | GAA | AAUACAAA | UUUGUAUUC UCCUUUGA |
| 30 | 7648 | GUUCAAAG | CUGAUGA | X   | GAA | AGAAUACA | UGUAUUCUC CUUUGAAC |
|    | 7651 | CGGGUUCA | CUGAUGA | X   | GAA | AGGAGAAU | AUUCUCCUU UGAACCCG |
|    | 7652 | ACGGGUUC | CUGAUGA | X   | GAA | AAGGAGAA | UUCUCCUUU GAACCCGU |
|    | 7661 | GAUGUUUU | CUGAUGA | X   | GAA | ACGGGUUC | GAACCCGUU AAAACAUC |

7662 GGAUGUUU CUGAUGA X GAA AACGGGUU AACCCGUUA AAACAUCC
7669 UGCCACAG CUGAUGA X GAA AUGUUUUA UAAAACAUC CUGUGGCA
Where "X" represents stem II region of a HH ribozyme (Hertel et al., 1992 Nucleic Acids Res. 20 3252). The length of stem II
5 may be ≥ 2 base-pairs.

Table III: Human flt1 VEGF Receptor-Hairpin Ribozyme and Substrate Sequence

|    |          |                     | DONDOR DARKERS SILVERS                           | 20120                |
|----|----------|---------------------|--|----------------------|
|    | nt.      |                     | HP Ribozyme Sequence                             | Substrate            |
|    | Position | u                   |  |                      |
|    | 16       | CGGGGAGG AGAA GAGAG | AGAA GAGAGG ACCAGAGAAACACGGUUGUGGUACAUUACCUGGUA  | כבחבתכפ פכח ככתככככפ |
| Ŋ  | 39       | CCGCUCCG AGAA GCCGC | AGAA GCCGCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGCGGCG GCU CGGAGCGG |
|    | 180      | CCGCCAGA AGAA GUCCU | AGAA GUCCUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAGGACG GAC UCUGGCGG |
|    | 190      | AACGACCC AGAA GCCAG | AGAA GCCAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | nance ecc eeencenn   |
|    | 278      | GCGCGCAC AGAA GGACC | AGAA GGACCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | agencen aen angegeec |
|    | 290      | GACAGCUG AGAA GCGCG | AGAA GCGCGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCGCGCU GCU CAGCUGUC |
| 10 | 295      | AAGCAGAC AGAA GAGCA | AGAA GAGCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CUGCUCA GCU GUCUGCUU |
|    | 298      | GAGAAGCA AGAA GCUGA | AGAA GCUGAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CUCAGCU GUC UGCUUCUC |
|    | 302      | CUGUGAGA AGAA GACAG | AGAA GACAGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCUGUCU GCU UCUCACAG |
|    | 420      | CAUUVAUG AGAA GCUUC | AGAA GCUUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGAAGCA GCC CAUAAAUG |
|    | 486      | CUUCCACA AGAA GAUUU | AGAA GAUUUA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UAAAUCU GCC UGUGGAAG |
| 15 | 537      | UUUGCUUG AGAA GUGUU | AGAA GUGUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAACACA GCU CAAGCAAA |
|    | 265      | AUAUUUGC AGAA GUAGA | AGAA GUAGAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UUCUACA GCU GCAAAUAU |
|    | 721      | CGUAACCC AGAA GGGAA | AGAA GGGAAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AUUCCCU GCC GGGUUACG |
|    | 786      | CGUUTUCC AGAA GGGAU | GGGAUC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA        | GAUCCCU GAU GGAAAACG |
|    | 863      | CUUCACAG AGAA GAAGC | AGAA GAAGCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA  | GGCUUCU GAC CUGUGAAG |

GAAAUCU GCU CGCUAUUU AACCCCA GAU UUACGAAA GUUUCCA GAC CCGCCUCU AGACCCG GCU CUCUACCC AAAUCCU GAC UUGUACCG UGUGGCU GAC UCUAGAAU UAUCACA GAU GUGCCAAA AAAUGCC GAC GGAAGGAG UVACCCU GAU GAAAAAA GCAAGCG GUC UUACCGGC CUUACCG GCU CUCUAUGA UGAAACU GUC UUGCACAG AUCAGCA GUU CCACCACU GCACGCU GUU UAUUGAAA AGCCUCA GAU CACUUGGU CCUCACU GUU CAAGGAAC CACUCUAA AAAGACU GAC UACCUAUC GGACCCA GAU GAAGUUCC UGGAGCU GAU UNUUUUUC AGAA GGGUAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCUUGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA AAAUAGCG AGAA GAUUUC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA UUUCGUAA AGAA GGGGUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGAAAC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGGUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCAUAGAG AGAA GGUAAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CGGUACAA AGAA GGAUUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AUUCUAGA AGAA GCCACA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GUGAUA ACCAGAGAAACACGGUGUGGGUACAUUACCUGGUA CUCCUUCC AGAA GCAUUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUGUGCAA AGAA GUUUCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGUGGUGG AGAA GCUGAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA ACCAAGUG AGAA GAGGCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UUUCAAUA AGAA GCGUGC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GUUCCUUG AGAA GUGAGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA JUAGAGUG AGAA GCUCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAUAGGUA AGAA GUCUUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGAACUUC AGAA GGGUCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA AGAA AGAGCCGG AGAA GGGUAGAG AGAA UUUGGCAC AGAA GCCGGUAA 1056 1310 1389 1535 1301 1566 1572 1604 1824 1908 1949 1973 2275 2525 2321 2396 2490 2625 2652

10

15

ഗ

GCACUCU GUU GGCCUCUC

GAGAGGCC AGAA GAGUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA

3995

15

GUGAGCG GCU CCCUUAUG GAC UGUGGCUG AAGCUCU GAU GACUGAGC GGCCUCU GAU GGUGAUUG GGAUUCU GAC GGUUUCUA UCUGACG GUU UCUACAAG GUU UUCAAGUG UNAACCU GCU GGGAGCCU AGCUCCG GCU UUCAGGAA AGUUCCU GUC UUCCAGAA GAU UAUGUGAG UUUUGCA GUC GCCUGAGG UCUAUCA GAU CAUGCUGG GCU GGCACAGA AAGAUCU GAU UUCUUACA AACUCCU GCC UUCUCUGA JAUTUCA GCU CCGAAGUU AAGCUCU GAU GAUGUCAG CGUGCCG UCUUACA CUGGACU GAACCCC CAUAAGGG AGAA GCUCAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGGCUCCC AGAA GGUUAA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGCACG ACCAGAGAACACGUUGUGGUACAUUACCUGGUA GAGCUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CAAUCACC AGAA GAGGCC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGAGCU ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA UAGAAACC AGAA GAAUCC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GUCAGA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA UGUAAGAA AGAA GAUCUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CACUUGAA AGAA GUAAGA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGAACU ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA CUCACAUA AGAA GGGUUC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CCUCAGGC AGAA GCAAAA ACCAGAAAACACACGUUGUGGUACAUUACCUGGUA UCAGAGAA AGAA GGAGUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AACUUCGG AGAA GAAAUA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CCAGCAUG AGAA GAUAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCUGUGCC AGAA GUCCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUGACAUC AGAA GAGCUU ACCAGAGAAACACGCUGUGGUACAUUACCUGGUA CAGCCACA AGAA UUCCUGAA AGAA UUCUGGAA AGAA GCUCAGUC AGAA CUUGUAGA AGAA 2816 3245 2873 2930 3157 3207 3256 3287 3402 3580 3655 3810 3846 3873 2684 2963 3211 3641

10

S

CGGGGCU GUC UGAUGUCA GCUGUCU GAU GUCAGCAG AGGCCCA GUU UCUGCCAU CAUUCCA GCU GUGGGCAC aceuecu ecu acacaeca GCUCCCC GCC CCCAGACU GGAGCCA GCU GCUUUUUG GCCCCCA GAC UACAACUC GCCAGCU GCU UUUUGUGA CUUCCCU GCU CCAACCCC AGGACCA GUU UGAUUGAG CUGCACU GAU CACCCAAU UGGGCCA GCC CUGCAGCC CCCUGCA GCC CAAAACCC CAGCUCU GAC CCUUCUAC GAU GGACAGCG GCU CUGACCCU JUAUUCU GUU UUGCACAG AAAUGCA GUC CUGAGGAG CUUCCCA AGGAGCA UGACAUCA AGAA GCCCCG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA CUGCUGAC AGAA GACAGC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA AGUCUGGG AGAA GGGAGC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GUGCCCAC AGAA GGAAUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCACGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GAGUUGUA AGAA GGGGGC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGGGUUGG AGAA GGGAAG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGCUCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA UCACAAAA AGAA GCUGGC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGUCCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AUUGGGUG AGAA GUGCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGCUGCAG AGAA GGCCCA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGGUUUUG AGAA GCAGGG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA AGGGUCAG AGAA GGGAAG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GUAGAAGG AGAA GAGCUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCUCCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUGUGCAA AGAA GAAUAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUCCUCAG AGAA GCAUUU ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGGCCU GGGCGGG AGAA AUGGCAGA AGAA CAAAAAGC AGAA CUCAAUCA AGAA CGCUGUCC AGAA 4100 4135 4104 4120 4210 4217 4385 4224 4382 4537 4573 4628 4594 4636 4905 4866 5233 4871 5281

10

15

വ

|    | 5319 | thuncence 7 | AGAA | gcccnc | AGAA GCCCUC ACCAGAGAACACACGIIIGIIGIIACAIIIJACCIIGGIIA | CACCCCII CAII CACCAAA |
|----|------|-------------|------|--------|---|-----------------------|
|    | 5358 |             | AGAA | gggncn | AGAA GGGUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | AGACCC GUC UCUAUACC   |
|    | 5392 |             | AGAA | GUGUUG | AGAA GUGUUG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA        | CAACACA GUU GGGACCCA  |
|    | 5563 | UGAGUCCC 1  | AGAA | GGAGAA | AGAA GGAGAA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA        | UUCUCCA GUU GGGACUCA  |
| Ŋ  | 5622 | AGUUUCAA 1  | AGAA | GUUGAA | AGAA GUUGAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UUCAACU GCU UUGAAACU  |
|    | 5738 | UAGCAUCA 1  | AGAA | GAGCCA | AGAA GAGCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UGGCUCU GUU UGAUGCUA  |
|    | 5838 | UAGCAUCA 1  | AGAA | GAGCCA | AGAA GAGCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UGGCUCU GUU UGAUGCUA  |
|    | 5933 | CCCCAAGA 1  | AGAA | GCAAUC | AGAA GCAAUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | GAUUGCU GCU UCUUGGGG  |
|    | 6022 | CACAUAAG 1  | AGAA | GAGGCA | AGAA GAGGCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UGCCUCU GUU CUUAUGUG  |
| 10 | 6120 | UCCACAAA 1  | AGAA | CCUGCC | AGAA GCUGCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA       | GGCAGCG GCU UUUGUGGA  |
|    | 6163 | GUGGAGAG 1  | AGAA | GUCCCA | AGAA GUCCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UGGGACA GUC CUCUCCAC  |
|    | 6270 | AAAUUGCC 1  | AGAA | GUCACA | AGAA GUCACA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UGUGACA GCU GGCAAUUU  |
|    | 6412 | AAGACAUG 1  | AGAA | GCUAAG | AGAA GCUAAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | cuvageu guv caugueuu  |
|    | 6511 | UUUGAAGG 1  | AGAA | GAGUAA | AGAA GAGUAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UVACUCA GCU CCUUCAAA  |
| 15 | 6778 | UCCACCCA 1  | AGAA | GUUCCA | AGAA GUUCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UGGAACA GUC UGGGUGGA  |
|    | 6826 | ACUUCUUG 1  | AGAA | GACAAG | AGAA GACAAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | CUUGUCA GUC CAAGAAGU  |
|    | 7245 | AACAUAAA 1  | AGAA | guugcc | AGAA GUUGCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | GGCAACU GCU UUUAUGUU  |
|    | 7258 | UGGAAGGA    | AGAA | GAACAU | AGAA GAACAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | AUGUNCU GUC UCCUUCCA  |
|    | 7433 | CCCAUACA 1  | AGAA | GCUAAA | AGAA GCUAAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA      | UUVAGCU GAU UGUAUGGG  |

## Table IV: Human KDR VEGF Receptor-Hammerhead Ribozyme and Substrate Sequence

|    | nt.   | HH Ribozyme        | Sequence     | Substrate          |
|----|-------|--------------------|--------------|--------------------|
| _  | Posi- |                    |              |                    |
| 5  | tion  |                    |              |                    |
|    | 21    | CACAGGGC CUGAUGA X | GAA ACGGCCAG | CUGGCCGUC GCCCUGUG |
|    | 33    | UCCACGCA CUGAUGA X | GAA AGCCACAG | CUGUGGCUC UGCGUGGA |
|    | 56    | AACCCACA CUGAUGA X | GAA AGGCGGCC | GGCCGCCUC UGUGGGUU |
|    | 64    | ACUAGGCA CUGAUGA X | GAA ACCCACAG | CUGUGGGUU UGCCUAGU |
| 10 | 65    | CACUAGGC CUGAUGA X | GAA AACCCACA | UGUGGGUUU GCCUAGUG |
|    | 70    | AGAAACAC CUGAUGA X | GAA AGGCAAAC | GUUUGCCUA GUGUUUCU |
|    | 75    | UCAAGAGA CUGAUGA X | GAA ACACUAGG | CCUAGUGUU UCUCUUGA |
|    | 76    | AUCAAGAG CUGAUGA X | GAA AACACUAG | CUAGUGUUU CUCUUGAU |
|    | 77    | GAUCAAGA CUGAUGA X | GAA AAACACUA | UAGUGUUUC UCUUGAUC |
| 15 | 79    | CAGAUCAA CUGAUGA X | GAA AGAAACAC | GUGUUUCUC UUGAUCUG |
|    | 81    | GGCAGAUC CUGAUGA X | GAA AGAGAAAC | GUUUCUCUU GAUCUGCC |
|    | 85    | CCUGGGCA CUGAUGA X | GAA AUCAAGAG | CUCUUGAUC UGCCCAGG |
|    | 96    | UGUAUGCU CUGAUGA X | GAA AGCCUGGG | CCCAGGCUC AGCAUACA |
|    | 102   | UCUUUUUG CUGAUGA X | GAA AUGCUGAG | CUCAGCAUA CAAAAAGA |
| 20 | 114   | AUUGUAAG CUGAUGA X | GAA AUGUCUUU | AAAGACAUA CUUACAAU |
|    | 117   | UUAAUUGU CUGAUGA X | GAA AGUAUGUC | GACAUACUU ACAAUUAA |
|    | 118   | CUUAAUUG CUGAUGA X | GAA AAGUAUGU | ACAUACUUA CAAUUAAG |
|    | 123   | UUAGCCUU CUGAUGA X | GAA AUUGUAAG | CUUACAAUU AAGGCUAA |
|    | 124   | AUUAGCCU CUGAUGA X | GAA AAUUGUAA | UUACAAUUA AGGCUAAU |
| 25 | 130   | AGUUGUAU CUGAUGA X | GAA AGCCUUAA | UUAAGGCUA AUACAACU |
|    | 133   | AAGAGUUG CUGAUGA X | GAA AUUAGCCU | AGGCUAAUA CAACUCUU |
|    | 139   | AAUUUGAA CUGAUGA X | gaa aguuguau | AUACAACUC UUCAAAUU |
|    | 141   | GUAAUUUG CUGAUGA X | GAA AGAGUUGU | ACAACUCUU CAAAUUAC |
|    | 142   | AGUAAUUU CUGAUGA X | GAA AAGAGUUG | CAACUCUUC AAAUUACU |
| 30 | 147   | CUGCAAGU CUGAUGA X | GAA AUUUGAAG | CUUCAAAUU ACUUGCAG |
|    | 148   | CCUGCAAG CUGAUGA X | GAA AAUUUGAA | UUCAAAUUA CUUGCAGG |
|    | 151   | UCCCCUGC CUGAUGA X | GAA AGUAAUUU | AAAUUACUU GCAGGGGA |

|    | 170 | GCCAGUCC CUGAUGA X GAA AGUCCCUC | GAGGGACUU GGACUGGC |
|----|-----|---------------------------------|--------------------|
|    | 180 | UUGGGCCA CUGAUGA X GAA AGCCAGUC | GACUGGCUU UGGCCCAA |
|    | 181 | AUUGGGCC CUGAUGA X GAA AAGCCAGU | ACUGGCUUU GGCCCAAU |
|    | 190 | ACUCUGAU CUGAUGA X GAA AUUGGGCC | GGCCCAAUA AUCAGAGU |
| 5  | 193 | GCCACUCU CUGAUGA X GAA AUUAUUGG | CCAAUAAUC AGAGUGGC |
|    | 243 | UUACAGAA CUGAUGA X GAA AGGCCAUC | GAUGGCCUC UUCUGUAA |
|    | 245 | UCUUACAG CUGAUGA X GAA AGAGGCCA | UGGCCUCUU CUGUAAGA |
|    | 246 | GUCUUACA CUGAUGA X GAA AAGAGGCC | GGCCUCUUC UGUAAGAC |
|    | 250 | GAGUGUCU CUGAUGA X GAA ACAGAAGA | UCUUCUGUA AGACACUC |
| 10 | 258 | GGAAUUGU CUGAUGA X GAA AGUGUCUU | AAGACACUC ACAAUUCC |
|    | 264 | ACUUUUGG CUGAUGA X GAA AUUGUGAG | CUCACAAUU CCAAAAGU |
|    | 265 | CACUUUUG CUGAUGA X GAA AAUUGUGA | UCACAAUUC CAAAAGUG |
|    | 276 | UCAUUUCC CUGAUGA X GAA AUCACUUU | AAAGUGAUC GGAAAUGA |
|    | 296 | AGCACUUG CUGAUGA X GAA AGGCUCCA | UGGAGCCUA CAAGUGCU |
| 15 | 305 | CCCGGUAG CUGAUGA X GAA AGCACUUG | CAAGUGCUU CUACCGGG |
|    | 306 | UCCCGGUA CUGAUGA X GAA AAGCACUU | AAGUGCUUC UACCGGGA |
|    | 308 | UUUCCCGG CUGAUGA X GAA AGAAGCAC | GUGCUUCUA CCGGGAAA |
|    | 323 | CCGAGGCC CUGAUGA X GAA AGUCAGUU | AACUGACUU GGCCUCGG |
|    | 329 | AAAUGACC CUGAUGA X GAA AGGCCAAG | CUUGGCCUC GGUCAUUU |
| 20 | 333 | ACAUAAAU CUGAUGA X GAA ACCGAGGC | GCCUCGGUC AUUUAUGU |
|    | 336 | UAGACAUA CUGAUGA X GAA AUGACCGA | UCGGUCAUU UAUGUCUA |
|    | 337 | AUAGACAU CUGAUGA X GAA AAUGACCG | CGGUCAUUU AUGUCUAU |
|    | 338 | CAUAGACA CUGAUGA X GAA AAAUGACC | GGUCAUUUA UGUCUAUG |
|    | 342 | UGAACAUA CUGAUGA X GAA ACAUAAAU | AUUUAUGUC UAUGUUCA |
| 25 | 344 | CUUGAACA CUGAUGA X GAA AGACAUAA | UUAUGUCUA UGUUCAAG |
|    | 348 | UAAUCUUG CUGAUGA X GAA ACAUAGAC | GUCUAUGUU CAAGAUUA |
|    | 349 | GUAAUCUU CUGAUGA X GAA AACAUAGA | UCUAUGUUC AAGAUUAC |
|    | 355 | AGAUCUGU CUGAUGA X GAA AUCUUGAA | UUCAAGAUU ACAGAUCU |
|    | 356 | GAGAUCUG CUGAUGA X GAA AAUCUUGA | UCAAGAUUA CAGAUCUC |
| 30 | 362 | UAAAUGGA CUGAUGA X GAA AUCUGUAA | UUACAGAUC UCCAUUUA |
|    | 364 | AAUAAAUG CUGAUGA X GAA AGAUCUGU | ACAGAUCUC CAUUUAUU |
|    | 368 | AAGCAAUA CUGAUGA X GAA AUGGAGAU | AUCUCCAUU UAUUGCUU |
|    | 369 | GAAGCAAU CUGAUGA X GAA AAUGGAGA | UCUCCAUUU AUUGCUUC |

|    | 370         | AGAAGCAA   | CUGAUGA | X | GAZ | AAAUGGAG | CUCCAUUUA   | ໜຣວນບວນ  |
|----|-------------|------------|---------|---|-----|----------|-------------|----------|
|    | 372         | ACAGAAGC   | CUGAUGA | X | GAZ | AUAÄAUGG | CCAUUUAUU   | GCUUCUGU |
|    | 376         | ACUAACAG   | CUGAUGA | x | GAA | AGCAAUAA | UUAUUGCUU   | CUGUUAGU |
|    | 377         | CACUAACA   | CUGAUGA | X | GAA | AAGCAAUA | UAUUGCUUC   | UGUUAGUG |
| 5  | 381         | UGGUCACU   | CUGAUGA | X | GAA | ACAGAAGC | GCUUCUGUU   | AGUGACCA |
|    | 382         | UUGGUCAC   | CUGAUGA | x | GAA | AACAGAAG | CUUCUGUUA   | GUGACCAA |
|    | <b>39</b> 9 | AUGUACAC   | CUGAUGA | X | GAA | ACUCCAUG | CAUGGAGUC   | GUGUACAU |
|    | 404         | CAGUAAUG   | CUGAUGA | x | GAA | ACACGACU | AGUCGUGUA   | CAUUACUG |
|    | 408         | UUCUCAGU   | CUGAUGA | x | GAA | AUGUACAC | GUGUACAUU   | ACUGAGAA |
| 10 | 409         | GUUCUCAG   | CUGAUGA | x | GAA | AAUGUACA | UGUACAUUA   | CUGAGAAC |
|    | 438         | AGACAUGG   | CUGAUGA | x | GAA | AUCACCAC | GUGGUGAUU   | CCAUGUCU |
|    | 439         | GAGACAUG   | CUGAUGA | X | GAA | AAUCACCA | UGGUGAUUC   | CAUGUCUC |
|    | 445         | GGACCCGA   | CUGAUGA | X | GAA | ACAUGGAA | UUCCAUGUC   | UCGGGUCC |
|    | 447         | AUGGACCC   | CUGAUGA | X | GAA | AGACAUGG | CCAUGUCUC   | GGGUCCAU |
| 15 | 452         | UUGAAAUG   | CUGAUGA | x | GAA | ACCCGAGA | UCUCGGGUC   | CAUUUCAA |
|    | 456         | AGAUUUGA   | CUGAUGA | x | GAA | AUGGACCC | GGGUCCAUU   | UCAAAUCU |
|    | 457         | GAGAUUUG   | CUGAUGA | x | GAA | AAUGGACC | GGUCCAUUU   | CAAAUCUC |
|    | 458         | UGAGAUUU   | CUGAUGA | x | GAA | AAAUGGAC | GUCCAUUUC   | AAAUCUCA |
|    | 463         | CACGUUGA ( | CUGAUGA | x | GAA | AUUUGAAA | UUUCAAAUC   | UCAACGUG |
| 20 | 465         | GACACGUU ( | CUGAUGA | x | GAA | AGAUUUGA | UCAAAUCUC   | AACGUGUC |
|    | 473         | CACAAAGU ( | CUGAUGA | X | GAA | ACACGUUG | CAACGUGUC   | ACUUUGUG |
|    | 477         | CUUGCACA ( | CUGAUGA | X | GAA | AGUGACAC | GUGUCACUU   | UGUGCAAG |
|    | 478         | UCUUGCAC ( | CUGAUGA | X | GAA | AAGUGACA | UGUCACUUU   | GUGCAAGA |
|    | 488         | UUUCUGGG ( | CUGAUGÁ | X | GAA | AUCUUGCA | UGCAAGAUA   | CCCAGAAA |
| 25 | 503         | CAGGAACA ( | CUGAUGA | X | GAA | AUCUCUUU | AAAGAGAUU   | UGUUCCUG |
|    | 504         | UCAGGAAC ( | CUGAUGA | X | GAA | AAUCUCUU | AAGAGAUUU   | GUUCCUGA |
|    | 507         | CCAUCAGG C | CUGAUGA | X | GAA | ACAAAUCU | AGAUUUGUU   | CCUGAUGG |
|    | 508         | ACCAUCAG ( | TUGAUGA | X | GAA | AACAAAUC | GAUUUGUUC   | CUGAUGGU |
|    | 517         | AAUUCUGU C | CUGAUGA | X | GAA | ACCAUCAG | CUGAUGGUA . | ACAGAAUU |
| 30 | 525         | UCCCAGGA C | CUGAUGA | X | GAA | AUUCUGUU | AACAGAAUU   | UCCUGGGA |
|    | 526         | GUCCCAGG C | TUGAUGA | X | GAA | AAUUCUGU | ACAGAAUUU   | CCUGGGAC |
|    | 527         | UGUCCCAG C | UGAUGA  | X | GAA | AAAUUCUG | CAGAAUUUC   | CUGGGACA |
|    | 548         | GAAUAGUA C | CUGAUGA | X | GAA | AGCCCUUC | GAAGGGCUU   | UACUAUUC |
|    |             |            |         |   |     |          |             |          |

|    | 549         | GGAAUAGU CUGAUGA X GAA AAGCCCUU | AAGGGCUUU ACUAUUCO |
|----|-------------|---------------------------------|--------------------|
|    | 550         | GGGAAUAG CUGAUGA X GAA AAAGCCCU | AGGGCUUUA CUAUUCCO |
|    | 553         | GCUGGGAA CUGAUGA X GAA AGUAAAGC | GCUUUACUA UUCCCAGO |
|    | <b>55</b> 5 | UAGCUGGG CUGAUGA X GAA AUAGUAAA | UUUACUAUU CCCAGCUA |
| 5  | 556         | GUAGCUGG CUGAUGA X GAA AAUAGUAA | UUACUAUUC CCAGCUAC |
|    | 563         | UGAUCAUG CUGAUGA X GAA AGCUGGGA | UCCCAGCUA CAUGAUCA |
|    | 570         | GCAUAGCU CUGAUGA X GAA AUCAUGUA | UACAUGAUC AGCUAUGC |
|    | 575         | UGCCAGCA CUGAUGA X GAA AGCUGAUC | GAUCAGCUA UGCUGGCA |
|    | 588         | UCACAGAA CUGAUGA X GAA ACCAUGCC | GGCAUGGUC UUCUGUGA |
| 10 | 590         | CUUCACAG CUGAUGA X GAA AGACCAUG | CAUGGUCUU CUGUGAAG |
|    | 591         | GCUUCACA CUGAUGA X GAA AAGACCAU | AUGGUCUUC UGUGAAGC |
|    | 606         | UCAUCAUU CUGAUGA X GAA AUUUUUGC | GCAAAAAUU AAUGAUGA |
|    | 607         | UUCAUCAU CUGAUGA X GAA AAUUUUUG | CAAAAAUUA AUGAUGAA |
|    | 619         | AGACUGGU CUGAUGA X GAA ACUUUCAU | AUGAAAGUU ACCAGUCU |
| 15 | 620         | UAGACUGG CUGAUGA X GAA AACUUUCA | UGAAAGUUA CCAGUCUA |
|    | 626         | ACAUAAUA CUGAUGA X GAA ACUGGUAA | UUACCAGUC UAUUAUGU |
|    | 628         | GUACAUAA CUGAUGA X GAA AGACUGGU | ACCAGUCUA UUAUGUAC |
|    | 630         | AUGUACAU CUGAUGA X GAA AUAGACUG | CAGUCUAUU AUGUACAU |
|    | 631         | UAUGUACA CUGAUGA X GAA AAUAGACU | AGUCUAUUA UGUACAUA |
| 20 | 635         | CAACUAUG CUGAUGA X GAA ACAUAAUA | UAUUAUGUA CAUAGUUG |
|    | 639         | ACGACAAC CUGAUGA X GAA AUGUACAU | AUGUACAUA GUUGUCGU |
|    | 642         | ACAACGAC CUGAUGA X GAA ACUAUGUA | UACAUAGUU GUCGUUGU |
|    | 645         | CCUACAAC CUGAUGA X GAA ACAACUAU | AUAGUUGUC GUUGUAGG |
|    | 648         | UACCCUAC CUGAUGA X GAA ACGACAAC | GUUGUCGUU GUAGGGUA |
| 25 | 651         | CUAUACCC CUGAUGA X GAA ACAACGAC | GUCGUUGUA GGGUAUAG |
|    | 656         | AAAUCCUA CUGAUGA X GAA ACCCUACA | UGUAGGGUA UAGGAUUU |
|    | 658         | AUAAAUCC CUGAUGA X GAA AUACCCUA | UAGGGUAUA GGAUUUAU |
|    | 663         | ACAUCAUA CUGAUGA X GAA AUCCUAUA | UAUAGGAUU UAUGAUGU |
|    | 664         | CACAUCAU CUGAUGA X GAA AAUCCUAU | AUAGGAUUU AUGAUGUG |
| 30 | 665         | CCACAUCA CUGAUGA X GAA AAAUCCUA | UAGGAUUUA UGAUGUGG |
|    | 675         | GGACUCAG CUGAUGA X GAA ACCACAUC | GAUGUGGUU CUGAGUCC |
|    | 676         | CGGACUCA CUGAUGA X GAA AACCACAU | AUGUGGUUC UGAGUCCG |
|    | 682         | AUGAGACG CUGAUGA X GAA ACUCAGAA | INICIAN CONTRACTOR |

PCT/US96/17480 WO 97/15662

|    | 686 | UUCCAUGA | CUGAUGA | x | GAA | ACGGACUC         | GAGUCCGUC | UCAUGGAA |
|----|-----|----------|---------|---|-----|------------------|-----------|----------|
|    | 688 | AAUUCCAU | CUGAUGA | x | GAA | AGACGGAC         | GUCCGUCUC | AUGGAAUU |
|    | 696 | GAUAGUUC | CUGAUGA | x | GAA | AUUCCAUG         | CAUGGAAUU | GAACUAUC |
|    | 702 | CCAACAGA | CUGAUGA | x | GAA | AGUUCAAU         | AUUGAACUA | UCUGUUGG |
| 5  | 704 | CUCCAACA | CUGAUGA | x | GAA | AUAGUUCA         | UGAACUAUC | UGUUGGAG |
|    | 708 | υυυυςυςς | CUGAUGA | x | GAA | ACAGAUAG         | CUAUCUGUU | GGAGAAAA |
|    | 720 | UUUAAGAC | CUGAUGA | x | GAA | AGCUUUUC         | GAAAAGCUU | GUCUUAAA |
|    | 723 | CAAUUUAA | CUGAUGA | x | GAA | ACAAGCUU         | AAGCUUGUC | UUAAAUUG |
|    | 725 | UACAAUUU | CUGAUGA | x | GAA | AGACAAGC         | GCUUGUCUU | AAAUUGUA |
| 10 | 726 | GUACAAUU | CUGAUGA | x | GAA | AAGACAAG         | CUUGUCUUA | AAUUGUAC |
|    | 730 | UGCUGUAC | CUGAUGA | X | GAA | AUUUAAGA         | UCUUAAAUU | GUACAGCA |
|    | 733 | UCUUGCUG | CUGAUGA | x | GAA | ACAAUUUA         | UAAAUUGUA | CAGCAAGA |
|    | 750 | CCCACAUU | CUGAUGA | x | GAA | AGUUCAGU         | ACUGAACUA | AAUGUGGG |
|    | 762 | UUGAAGUC | CUGAUGA | x | GAA | AUCCCCAC         | GUGGGGAUU | GACUUCAA |
| 15 | 767 | CCCAGUUG | CUGAUGA | x | GAA | AGUCAAUC         | GAUUGACUU | CAACUGGG |
|    | 768 | UCCCAGUU | CUGAUGA | x | GAA | AAGUCAAU         | AUUGACUUC | AACUGGGA |
|    | 779 | AAGAAGGG | CUGAUGA | x | GAA | AUUCCCAG         | CUGGGAAUA | CCCUUCUU |
|    | 784 | CUUCGAAG | CUGAUGA | x | GAA | AGGGUAUU         | AAUACCCUU | CUUCGAAG |
|    | 785 | GCUUCGAA | CUGAUGA | x | GAA | <b>AAGGGU</b> AU | AUACCCUUC | UUCGAAGC |
| 20 | 787 | AUGCUUCG | CUGAUGA | x | GAA | AGAAGGGU         | ACCCUUCUU | CGAAGCAU |
|    | 788 | GAUGCUUC | CUGAUGA | x | GAA | AAGAAGGG         | cccuucuuc | GAAGCAUC |
|    | 796 | CUUAUGCU | CUGAUGA | x | GAA | AUGCUUCG         | CGAAGCAUC | AGCAUAAG |
|    | 802 | AAGUUUCU | CUGAUGA | x | GAA | AUGCUGAU         | AUCAGCAUA | AGAAACUU |
|    | 810 | CGGUUUAC | CUGAUGA | x | GAA | AGUUUCUU         | AAGAAACUU | GUAAACCG |
| 25 | 813 | UCUCGGUU | CUGAUGA | x | GAA | ACAAGUUU         | AAACUUGUA | AACCGAGA |
|    | 825 | UGGGUUUU | CUGAUGA | x | GAA | AGGUCUCG         | CGAGACCUA | AAAACCCA |
|    | B36 | CACUCCCA | CUGAUGA | x | GAA | ACUGGGUU         | AACCCAGUC | UGGGAGUG |
|    | 857 | UGCUCAAA | CUGAUGA | x | GAA | AUUUCUUC         | GAAGAAAUU | UUUGAGCA |
|    | 858 | GUGCUCAA | CUGAUGA | X | GAA | AAUUUCUU         | AAGAAAUUU | UUGAGCAC |
| 30 | 859 | GGUGCUCA | CUGAUGA | X | GAA | AAAUUUCU         | AGAAAUUUU | UGAGCACC |
|    | 860 | AGGUGCUC | CUGAUGA | x | GAA | AAAAUUUC         | GAAAUUUUU | GAGCACCU |
|    | 869 | CUAUAGUU | CUGAUGA | x | GAA | AGGUGCUC         | GAGCACCUU | AACUAUAG |
|    | 870 | UCUAUAGU | CUGAUGA | x | GAA | AAGGUGCU         | AGCACCUUA | ACUAUAGA |

|    | 874  | ACCAUCUA  | CUGAUGA | X | GAA | AGUUAAGG  | CCUUAACUA  | UAGAUGGU |
|----|------|-----------|---------|---|-----|-----------|------------|----------|
|    | 876  | ACACCAUC  | CUGAUGA | x | GAA | AUAGUUAA  | UUAACUAUA  | GAUGGUGU |
|    | 885  | CUCCGGGU  | CUGAUGA | X | GAA | ACACCAUC  | GAUGGUGUA  | ACCCGGAG |
|    | 905  | AGGUGUAC  | CUGAUGA | X | GAA | AUCCUUGG  | CCAAGGAUU  | GUACACCU |
| 5  | 908  | CACAGGUG  | CUGAUGA | X | GAA | ACAAUCCU  | AGGAUUGUA  | CACCUGUG |
|    | 923  | GCCCACUG  | CUGAUGA | X | GAA | AUGCUGCA  | UGCAGCAUC  | CAGUGGGC |
|    | 956  | CCCUGACA  | CUGAUGA | X | GAA | AUGUGCUG  | CAGCACAUU  | UGUCAGGG |
|    | 957  | ACCCUGAC  | CUGAUGA | x | GAA | AAUGUGCU  | AGCACAUUU  | GUCAGGGU |
|    | 960  | UGGACCCU  | CUGAUGA | x | GAA | ACAAAUGU  | ACAUUUGUC  | AGGGUCCA |
| 10 | 966  | UUUUCAUG  | CUGAUGA | X | GAA | ACCCUGAC  | GUCAGGGUC  | CAUGAAAA |
|    | 979  | AGCAACAA  | CUGAUGA | X | GAA | AGGUUUUU  | AAAAACCUU  | UUGUUGCU |
|    | 980  | AAGCAACA  | CUGAUGA | X | GAA | AAGGUUUU  | AAAACCUUU  | UGUUGCUU |
|    | 981  | AAAGCAAC  | CUGAUGA | x | GAA | AAAGGUUU  | AAACCUUUU  | GUUGCUUU |
|    | 984  | CCAAAAGC  | CUGAUGA | x | GAA | ACAAAAGG  | ccuuuuguu  | GCUUUUGG |
| 15 | 988  | ACUUCCAA  | CUGAUGA | X | GAA | AGCAACAA  | UUGUUGCUU  | UUGGAAGU |
|    | 989  | CACUUCCA  | CUGAUGA | X | GAA | AAGCAACA  | UGUUGCUUU  | UGGAAGUG |
|    | 990  | CCACUUCC  | CUGAUGA | X | GAA | AAAGCAAC  | GUUGCUUUU  | GGAAGUGG |
|    | 1007 | CCACCAGA  | CUGAUGA | x | GAA | AUUCCAUG  | CAUGGAAUC  | UCUGGUGG |
|    | 1009 | UUCCACCA  | CUGAUGA | X | GAA | AGAUUCCA  | UGGAAUCUC  | UGGUGGAA |
| 20 | 1038 | GGGAUUCU  | CUGAUGA | x | GAA | ACACGCUC  | GAGCGUGUC  | AGAAUCCC |
|    | 1044 | UUCGCAGG  | CUGAUGA | x | GAA | AUUCUGAC  | GUCAGAAUC  | CCUGCGAA |
|    | 1055 | AACCAAGG  | CUGAUGA | X | GAA | ACUUCGCA  | UGCGAAGUA  | CCUUGGUU |
|    | 1059 | GGGUAACC  | CUGAUGA | X | GAA | AGGUACUU  | AAGUACCUU  | GGUUACCC |
|    | 1063 | GGGUGGGU  | CUGAUGA | X | GAA | ACCAAGGU  | ACCUUGGUU  | ACCCACCC |
| 25 | 1064 | GGGGUGGG  | CUGAUGA | X | GAA | AACCAAGG  | CCUUGGUUA  | CCCACCCC |
|    | 1080 | UACCAUUU  | CUGAUGA | X | GAA | AUUUCUGG  | CCAGAAAUA  | AAAUGGUA |
|    | 1088 | CAUUUUUA  | CUGAUGA | X | GAA | ACCAUUUU  | AAAAUGGUA  | UAAAAAUG |
|    | 1090 | UCCAUUUU  | CUGAUGA | X | GAA | AUACCAUU  | AAUGGUAUA  | Aaaaugga |
|    | 1101 | UCAAGGGG  | CUGAUGA | x | GAA | AUUCCAUU  | AAUGGAAUA  | CCCCUUGA |
| 30 | 1107 | UUGGACUC  | CUGAUGA | x | GAA | AGGGGUAU  | AUACCCCUU  | GAGUCCAA |
|    | 1112 | UGUGAUUG  | CUGAUGA | X | GAA | ACUCAAGG  | CCUUGAGUC  | CAAUCACA |
|    | 1117 | AAUUGUGU  | CUGAUGA | x | GAA | AUUGGACU  | AGUCCAAUC  | ACACAAUU |
|    | 1125 | CCCGCUUUI | CUGAUGA | x | GAA | AUTIGUEUG | САСАСАВІПІ | AAACCCCC |

|    | 1126 | ccccccuu | CUGAUGA | X   | GAA | AAUUGUGU   | ACACAAUU  | AAGCGGGG   |
|----|------|----------|---------|-----|-----|------------|-----------|------------|
|    | 1140 | AUCGUCAG | CUGAUGA | X   | GAA | ACAUGCCC   | GGGCAUGU  | CUGACGAU   |
|    | 1149 | ACUUCCAU | CUGAUGA | X A | GAA | AUCGUCAG   | CUGACGAU  | J AUGGAAGU |
|    | 1150 | CACUUCCA | CUGAUGA | x x | GAA | AAUCGUCA   | UGACGAUUA | UGGAAGUG   |
| 5  | 1180 | GACAGUGU | CUGAUGA | X   | GAA | AUUUCCUG   | CAGGAAAUU | ACACUGUC   |
|    | 1181 | UGACAGUG | CUGAUGA | X   | GAA | AAUUUCCU   | AGGAAAUUA | CACUGUCA   |
|    | 1188 | GUAAGGAU | CUGAUGA | X   | GAA | ACAGUGUA   | UACACUGUO | AUCCUUAC   |
|    | 1191 | UUGGUAAG | CUGAUGA | X   | gaa | AUGACAGU   | ACUGUCAUC | CUUACCAA   |
|    | 1194 | GGAUUGGU | CUGAUGA | x   | GAA | AGGAUGAC   | GUCAUCCUU | ACCAAUCC   |
| 10 | 1195 | GGGAUUGG | CUGAUGA | x   | GAA | AAGGAUGA   | UCAUCCUUA | CCAAUCCC   |
|    | 1201 | UGAAAUGG | CUGAUGA | x   | GAA | AUUGGUAA   | UUACCAAUC | CCAUUUCA   |
|    | 1206 | UCCUUUGA | CUGAUGA | x   | GAA | AUGGGAUU   | AAUCCCAUU | UCAAAGGA   |
|    | 1207 | CUCCUUUG | CUGAUGA | x   | GAA | AAUGGGAU   | AUCCCAUUU | CAAAGGAG   |
|    | 1208 | UCUCCUUU | CUGAUGA | x   | GAA | AAAUGGGA   | UCCCAUUUC | AAAGGAGA   |
| 15 | 1233 | ACCAGAGA | CUGAUGA | x   | GAA | ACCACAUG   | CAUGUGGUC | UCUCUGGU   |
|    | 1235 | CAACCAGA | CUGAUGA | X   | GAA | AGACCACA   | UGUGGUCUC | UCUGGUUG   |
|    | 1237 | CACAACCA | CUGAUGA | x   | GAA | AGAGACCA   | UGGUCUCUC | UGGUUGUG   |
|    | 1242 | ACAUACAC | CUGAUGA | x   | GAA | ACCAGAGA   | UCUCUGGUU | GUGUAUGU   |
|    | 1247 | GUGGGACA | CUGAUGA | x   | GAA | ACACAACC   | GGUUGUGUA | UGUCCCAC   |
| 20 | 1251 | UGGGGUGG | CUGAUGA | x   | GAA | ACAUACAC   | GUGUAUGUC | CCACCCCA   |
|    | 1263 | UUCUCACC | CUGAUGA | x   | GAA | AUCUGGGG   | CCCCAGAUU | GGUGAGAA   |
|    | 1274 | AGAUUAGA | CUGAUGA | х   | GAA | AUUUCUCA   | UGAGAAAUC | UCUAAUCU   |
|    | 1276 | AGAGAUUA | CUGAUGA | x   | GAA | AGAUUUCU   | AGAAAUCUC | UAAUCUCU   |
|    | 1278 | GGAGAGAU | CUGAUGA | X   | GAA | AGAGAUUU . | AAAUCUCUA | AUCUCUCC   |
| 25 | 1281 | ACAGGAGA | CUGAUGA | X   | GAA | AUUAGAGA   | UCUCUAAUC | UCUCCUGU   |
|    | 1283 | CCACAGGA | CUGAUGA | X   | GAA | AGAUUAGA   | UCUAAUCUC | UCCUGUGG   |
|    | 1285 | AUCCACAG | CUGAUGA | X   | GAA | AGAGAUUA   | UAAUCUCUC | CUGUGGAU   |
|    | 1294 | CUGGUAGG | CUGAUGA | X   | GAA | AUCCACAG   | CUGUGGAUU | CCUACCAG   |
|    | 1295 | ACUGGUAG | CUGAUGA | X   | GAA | AAUCCACA   | UGUGGAUUC | CUACCAGU   |
| 30 | 1298 | CGUACUGG | CUGAUGA | X   | GAA | AGGAAUCC   | GGAUUCCUA | CCAGUACG   |
|    | 1304 | UGGUGCCG | CUGAUGA | x   | GAA | ACUGGUAG   | CUACCAGUA | CGGCACCA   |
|    | 1315 | CAGCGUUU | CUGAUGA | x   | GAA | AGUGGUGC   | GCACCACUC | AAACGCUG   |
|    | 1330 | AUAGACCG | CUGAUGA | x   | GAA | ACAUGUCA   | UGACAUGUA | CGGUCUAU   |

|    | 1335 | AUGGCAUA  | CUGAUGA | X          | GAA | ACCGUACA  | UGUACGGUC | UAUGCCAU |
|----|------|-----------|---------|------------|-----|-----------|-----------|----------|
|    | 1337 | GAAUGGCA  | CUGAUGA | . х        | GAA | AGACCGUA  | UACGGUCUA | UGCCAUUC |
|    | 1344 | GGGGGAGG  | CUGAUGA | . <b>x</b> | GAA | AUGGCAUA  | UAUGCCAUU | ccuccccc |
|    | 1345 | CGGGGGAG  | CUGAUGA | X          | GAA | AAUGGCAU  | AUGCCAUUC | CUCCCCCG |
| 5  | 1348 | AUGCGGGG  | CUGAUGA | X          | GAA | AGGAAUGG  | CCAUUCCUC | CCCCGCAU |
|    | 1357 | GUGGAUGU  | CUGAUGA | X          | GAA | AUGCGGGG  | CCCCGCAUC | ACAUCCAC |
|    | 1362 | UACCAGUG  | CUGAUGA | X          | GAA | AUGUGAUG  | CAUCACAUC | CACUGGUA |
|    | 1370 | ACUGCCAA  | CUGAUGA | X          | GAA | ACCAGUGG  | CCACUGGUA | UUGGCAGU |
|    | 1372 | CAACUGCC  | CUGAUGA | X          | GAA | AUACCAGU  | ACUGGUAUU | GGCAGUUG |
| 10 | 1379 | cuuccucc  | CUGAUGA | x          | GAA | ACUGCCAA  | UUGGCAGUU | GGAGGAAG |
|    | 1416 | GUCACUGA  | CUGAUGA | X          | GAA | ACAGCUUG  | CAAGCUGUC | UCAGUGAC |
|    | 1418 | UUGUCACU  | CUGAUGA | x          | GAA | AGACAGCU  | AGCUGUCUC | AGUGACAA |
|    | 1433 | CACAAGGG  | CUGAUGA | x          | GAA | AUGGGUUU  | AAACCCAUA | CCCUUGUG |
|    | 1438 | UUCUUCAC  | CUGAUGA | x          | GAA | AGGGUAUG  | CAUACCCUU | GUGAAGAA |
| 15 | 1466 | CUCCCUGG  | CUGAUGA | x          | GAA | AGUCCUCC  | GGAGGACUU | CCAGGGAG |
|    | 1467 | CCUCCCUG  | CUGAUGA | x          | GAA | AAGUCCUC  | GAGGACUUC | CAGGGAGG |
|    | 1480 | UUCAAUUU  | CUGAUGA | X          | GAA | AUUUCCUC  | GAGGAAAUA | AAAUUGAA |
|    | 1485 | UUAACUUC  | CUGAUGA | X          | GAA | UUAUUUA   | UUAAAAUU  | GAAGUUAA |
|    | 1491 | UUAUUUUU  | CUGAUGA | X          | GAA | ACUUCAAU  | AUUGAAGUU | AAUAAAA  |
| 20 | 1492 | UAUUUUUAU | CUGAUGA | X          | GAA | AACUUCAA  | UUGAAGUUA | UAAAAAU  |
|    | 1495 | UUGAUUUU  | CUGAUGA | X          | GAA | AUUAACUU  | AAGUUAAUA | AAAAUCAA |
|    | 1501 | AGCAAAUU  | CUGAUGA | X          | GAA | UAUUUUUAU | AUAAAAAUC | AAUUUGCU |
|    | 1505 | UUAGAGCA  | CUGAUGA | X          | GAA | AUUGAUUU  | AAAUCAAUU | UGCUCUAA |
|    | 1506 | AUUAGAGC  | CUGAUGA | X          | GAA | AAUUGAUU  | AAUCAAUUU | GCUCUAAU |
| 25 | 1510 | UUCAAUUA  | CUGAUGA | X          | GAA | AGCAAAUU  | AAUUUGCUC | UAAUUGAA |
|    | 1512 | CCUUCAAU  | CUGAUGA | X          | GAA | AGAGCAAA  | UUUGCUCUA | AUUGAAGG |
|    | 1515 | UUUCCUUC  | CUGAUGA | X          | GAA | AUUAGAGC  | GCUCUAAUU | GAAGGAAA |
|    | 1536 | AGGGUACU  | CUGAUGA | X          | GAA | ACAGUUUU  | AAAACUGUA | AGUACCCU |
|    | 1540 | AACAAGGG  | CUGAUGA | X          | GAA | ACUUACAG  | CUGUAAGUA | cccuuguu |
| 30 | 1545 | UGGAUAAC  | CUGAUGA | X          | GAA | AGGGUACU  | AGUACCCUU | GUUAUCCA |
|    | 1548 | GCUUGGAU  | CUGAUGA | X          | GAA | ACAAGGGU  | ACCCUUGUU | AUCCAAGC |
|    | 1549 | CGCUUGGA  | CUGAUGA | X          | GAA | AACAAGGG  | CCCUUGUUA | UCCAAGCG |
|    | 1551 | GCCGCUUG  | CUGAUGA | X          | GAA | AUAACAAG  | CUUGUUAUC | CAAGCGGC |
|    |      |           |         |            |     |           |           |          |

PCT/US96/17480 WO 97/15662

|    | 1568 | ACAAAGCU | CUGAUGA | X | GAA | ACACAUUU | AAAUGUGUC | AGCUUUGU |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 1573 | UUUGUACA | CUGAUGA | X | GAA | AGCUGACA | UGUCAGCUU | UGUACAAA |
|    | 1574 | AUUUGUAC | CUGAUGA | X | GAA | AAGCUGAC | GUCAGCUUU | GUACAAAU |
|    | 1577 | CACAUUUG | CUGAUGA | x | GAA | ACAAAGCU | AGCUUUGUA | CAAAUGUG |
| 5  | 1593 | ACUUUGUU | CUGAUGA | x | GAA | ACCGCUUC | GAAGCGGUC | AACAAAGU |
|    | 1602 | ccucuccc | CUGAUGA | X | GAA | ACUUUGUU | AACAAAGUC | GGGAGAGG |
|    | 1623 | UGGAAGGA | CUGAUGA | X | GAA | AUCACCCU | AGGGUGAUC | UCCUUCCA |
|    | 1625 | CGUGGAAG | CUGAUGA | X | GAA | AGAUCACC | GGUGAUCUC | CUUCCACG |
|    | 1628 | UCACGUGG | CUGAUGA | x | GAA | AGGAGAUC | GAUCUCCUU | CCACGUGA |
| 10 | 1629 | GUCACGUG | CUGAUGA | x | GAA | AAGGAGAU | AUCUCCUUC | CACGUGAC |
|    | 1645 | AAUUUCAG | CUGAUGA | x | GAA | ACCCCUGG | CCAGGGGUC | CUGAAAUU |
|    | 1653 | UGCAAAGU | CUGAUGA | x | GAA | AUUUCAGG | CCUGAAAUU | ACUUUGCA |
|    | 1654 | UUGCAAAG | CUGAUGA | x | GAA | AAUUUCAG | CUGAAAUUA | CUUUGCAA |
|    | 1657 | AGGUUGCA | CUGAUGA | x | GAA | AGUAAUUU | AAAUUACUU | UGCAACCU |
| 15 | 1658 | CAGGUUGC | CUGAUGA | x | GAA | AAGUAAUU | AAUUACUUU | GCAACCUG |
|    | 1697 | ACCACAAA | CUGAUGA | X | GAA | ACACGCUC | GAGCGUGUC | UUUGUGGU |
|    | 1699 | GCACCACA | CUGAUGA | x | GAA | AGACACGC | GCGUGUCUU | UGUGGUGC |
|    | 1700 | UGCACCAC | CUGAUGA | x | GAA | AAGACACG | CGUGUCUUU | GUGGUGCA |
|    | 1721 | CAAACGUA | CUGAUGA | x | GAA | AUCUGUCU | AGACAGAUC | UACGUUUG |
| 20 | 1723 | CUCAAACG | CUGAUGA | x | GAA | AGAUCUGU | ACAGAUCUA | CGUUUGAG |
|    | 1727 | GGUUCUCA | CUGAUGA | X | GAA | ACGUAGAU | AUCUACGUU | UGAGAACC |
|    | 1728 | AGGUUCUC | CUGAUGA | X | GAA | AACGUAGA | UCUACGUUU | GAGAACCU |
|    | 1737 | UACCAUGU | CUGAUGA | X | GAA | AGGUUCUC | GAGAACCUC | ACAUGGUA |
|    | 1745 | CAAGCUUG | CUGAUGA | X | GAA | ACCAUGUG | CACAUGGUA | CAAGCUUG |
| 25 | 1752 | UGUGGGCC | CUGAUGA | X | GAA | AGCUUGUA | UACAAGCUU | GGCCCACA |
|    | 1765 | GAUUGGCA | CUGAUGA | x | GAA | AGGCUGUG | CACAGCCUC | UGCCAAUC |
|    | 1773 | CCCACAUG | CUGAUGA | X | GAA | AUUGGCAG | CUGCCAAUC | CAUGUGGG |
|    | 1787 | GUGUGGGC | CUGAUGA | X | GAA | ACUCUCCC | GGGAGAGUU | GCCCACAC |
|    | 1800 | UUCUUGCA | CUGAUGA | x | GAA | ACAGGUGU | ACACCUGUU | UGCAAGAA |
| 30 | 1801 | GUUCUUGC | CUGAUGA | x | GAA | AACAGGUG | CACCUGUUU | GCAAGAAC |
|    | 1811 | GAGUAUCC | CUGAUGA | x | GAA | AGUUCUUG | CAAGAACUU | GGAUACUC |
|    | 1816 | CCAAAGAG | CUGAUGA | x | GAA | AUCCAAGU | ACUUGGAUA | CUCUUUGG |
|    | 1819 | UUUCCAAA | CUGAUGA | x | GAA | AGUAUCCA | UGGAUACUC | UUUGGAAA |

|    | 1821 | AAUUUCCA CUGAUGA X GAA AGAGUAUC | GAUACUCUU UGGAAAUU |
|----|------|---------------------------------|--------------------|
|    | 1822 | CAAUUUCC CUGAUGA X GAA AAGAGUAU |                    |
|    | 1829 | UGGCAUUC CUGAUGA X GAA AUUUCCAA |                    |
|    | 1844 | UAUUAGAG CUGAUGA X GAA ACAUGGUG |                    |
| 5  | 1845 | CUAUUAGA CUGAUGA X GAA AACAUGGU |                    |
|    | 1847 | UGCUAUUA CUGAUGA X GAA AGAACAUG | CAUGUUCUC UAAUAGCA |
|    | 1849 | UGUGCUAU CUGAUGA X GAA AGAGAACA |                    |
|    | 1852 | AUUUGUGC CUGAUGA X GAA AUUAGAGA | UCUCUAAUA GCACAAAU |
|    | 1866 | AUGAUCAA CUGAUGA X GAA AUGUCAUU | AAUGACAUU UUGAUCAU |
| 10 | 1867 | CAUGAUCA CUGAUGA X GAA AAUGUCAU | AUGACAUUU UGAUCAUG |
|    | 1868 | CCAUGAUC CUGAUGA X GAA AAAUGUCA | UGACAUUUU GAUCAUGG |
|    | 1872 | AGCUCCAU CUGAUGA X GAA AUCAAAAU | AUUUUGAUC AUGGAGCU |
|    | 1881 | GCAUUCUU CUGAUGA X GAA AGCUCCAU | AUGGAGCUU AAGAAUGC |
|    | 1882 | UGCAUUCU CUGAUGA X GAA AAGCUCCA | UGGAGCUUA AGAAUGCA |
| 15 | 1892 | CCUGCAAG CUGAUGA X GAA AUGCAUUC | GAAUGCAUC CUUGCAGG |
|    | 1895 | GGUCCUGC CUGAUGA X GAA AGGAUGCA | UGCAUCCUU GCAGGACC |
|    | 1913 | GGCAGACA CUGAUGA X GAA AGUCUCCU | AGGAGACUA UGUCUGCC |
|    | 1917 | GCAAGGCA CUGAUGA X GAA ACAUAGUC | GACUAUGUC UGCCUUGC |
|    | 1923 | UCUUGAGC CUGAUGA X GAA AGGCAGAC | GUCUGCCUU GCUCAAGA |
| 20 | 1927 | CCUGUCUU CUGAUGA X GAA AGCAAGGC | GCCUUGCUC AAGACAGG |
|    | 1954 | GACCACGC CUGAUGA X GAA AUGUCUUU | AAAGACAUU GCGUGGUC |
|    | 1962 | AGCUGCCU CUGAUGA X GAA ACCACGCA | UGCGUGGUC AGGCAGCU |
|    | 1971 | AGGACUGU CUGAUGA X GAA AGCUGCCU | AGGCAGCUC ACAGUCCU |
| 25 | 1977 | CGCUCUAG CUGAUGA X GAA ACUGUGAG | CUCACAGUC CUAGAGCG |
| 25 | 1980 | ACACGCUC CUGAUGA X GAA AGGACUGU | ACAGUCCUA GAGCGUGU |
|    | 2001 | UUUCCUGU CUGAUGA X GAA AUCGUGGG | CCCACGAUC ACAGGAAA |
|    | 2020 | UGUCGUCU CUGAUGA X GAA AUUCUCCA | UGGAGAAUC AGACGACA |
|    | 2032 | UUCCCCAA CUGAUGA X GAA ACUUGUCG | CGACAAGUA UUGGGGAA |
| 20 | 2034 | CUUUCCCC CUGAUGA X GAA AUACUUGU | ACAAGUAUU GGGGAAAG |
| 30 | 2046 |                                 | GAAAGCAUC GAAGUCUC |
|    | 2052 | GUGCAUGA CUGAUGA X GAA ACUUCGAU | Caroomic           |
|    | 2054 | CCGUGCAU CUGAUGA X GAA AGACUUCG | CGAAGUCUC AUGCACGG |
|    | 2066 | GAUUCCCA CUGAUGA X GAA AUGCCGUG | CACGGCAUC UGGGAAUC |

PCT/US96/17480

107

WO 97/15662

|    | 2074 | UGGAGGGG | CUGAUGA | X | GAA | AUUCCCAG | CUGGGAAUC | CCCCUCCA |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 2080 | GAUCUGUG | CUGAUGA | X | GAA | AGGGGGAU | AUCCCCCUC | CACAGAUC |
|    | 2088 | AACCACAU | CUGAUGA | X | GAA | AUCUGUGG | CCACAGAUC | AUGUGGUU |
|    | 2096 | UAUCUUUA | CUGAUGA | X | GAA | ACCACAUG | CAUGUGGUU | UAAAGAUA |
| 5  | 2097 | UUAUCUUU | CUGAUGA | X | GAA | AACCACAU | AUGUGGUUU | AAAGAUAA |
|    | 2098 | AUUAUCUU | CUGAUGA | X | GAA | AAACCACA | UGUGGUUUA | AAGAUAAU |
|    | 2104 | GGUCUCAU | CUGAUGA | X | GAA | AUCUUUAA | UUAAAGAUA | AUGAGACC |
|    | 2115 | UCUUCUAC | CUGAUGA | X | GAA | AGGGUCUC | GAGACCCUU | GUAGAAGA |
|    | 2118 | GAGUCUUC | CUGAUGA | X | GAA | ACAAGGGU | ACCCUUGUA | GAAGACUC |
| 10 | 2126 | CAAUGCCU | CUGAUGA | X | GAA | AGUCUUCU | AGAAGACUC | AGGCAUUG |
|    | 2133 | UUCAAUAC | CUGAUGA | X | GAA | AUGCCUGA | UCAGGCAUU | GUAUUGAA |
|    | 2136 | UCCUUCAA | CUGAUGA | X | GAA | ACAAUGCC | GGCAUUGUA | UUGAAGGA |
|    | 2138 | CAUCCUUC | CUGAUGA | x | GAA | AUACAAUG | CAUUGUAUU | GAAGGAUG |
|    | 2160 | CGGAUAGU | CUGAUGA | X | GAA | AGGUUCCG | CGGAACCUC | ACUAUCCG |
| 15 | 2164 | UCUGCGGA | CUGAUGA | X | GAA | AGUGAGGU | ACCUCACUA | UCCGCAGA |
|    | 2166 | ACUCUGCG | CUGAUGA | X | GAA | AUAGUGAG | CUCACUAUC | CGCAGAGU |
|    | 2196 | CAGGUGUA | CUGAUGA | X | GAA | AGGCCUUC | GAAGGCCUC | UACACCUG |
|    | 2198 | GGCAGGUG | CUGAUGA | X | GAA | AGAGGCCU | AGGCCUCUA | CACCUGCC |
|    | 2220 | CAGCCAAG | CUGAUGA | X | GAA | ACACUGCA | UGCAGUGUU | CUUGGCUG |
| 20 | 2221 | ACAGCCAA | CUGAUGA | X | GAA | AACACUGC | GCAGUGUUC | UUGGCUGU |
|    | 2223 | GCACAGCC | CUGAUGA | X | GAA | AGAACACU | AGUGUUCUU | GGCUGUGC |
|    | 2246 | UUAUGAAA | CUGAUGA | X | GAA | AUGCCUCC | GGAGGCAUU | UUUCAUAA |
|    | 2247 | AUUAUGAA | CUGAUGA | X | GAA | AAUGCCUC | GAGGCAUUU | UUCAUAAU |
|    | 2248 | UAUUAUGA | CUGAUGA | X | GAA | AAAUGCCU | AGGCAUUUU | UCAUAAUA |
| 25 | 2249 | CUAUUAUG | CUGAUGA | X | GAA | AAAAUGCC | GGCAUUUUU | CAUAAUAG |
|    | 2250 | UCUAUUAU | CUGAUGA | X | GAA | AAAAAUGC | GCAUUUUUC | AUAAUAGA |
|    | 2253 | CCUUCUAU | CUGAUGA | X | GAA | AUGAAAAA | UUUUUCAUA | AUAGAAGG |
|    | 2256 | GCACCUUC | CUGAUGA | X | GAA | AUUAUGAA | UUCAUAAUA | GAAGGUGC |
|    | 2282 | UGAUUUCC | CUGAUGA | X | GAA | AGUUCGUC | GACGAACUU | GGAAAUCA |
| 30 | 2289 | AGAAUAAU | CUGAUGA | X | GAA | AUUUCCAA | UUGGAAAUC | AUUAUUCU |
|    | 2292 | ACUAGAAU | CUGAUGA | X | GAA | AUGAUUUC | GAAAUCAUU | AUUCUAGU |
|    | 2293 | UACUAGAA | CUGAUGA | X | GAA | AAUGAUUU | AAAUCAUUA | UUCUAGUA |
|    | 2295 | CCUACUAG | CUGAUGA | X | GAA | AUAAUGAU | AUCAUUAUU | CUAGUAGG |
|    |      |          |         |   |     |          |           |          |

|    | 2296 | GCCUACUA CUGAUGA X GAA AAUAAUGA | UCAUUAUUC UAGUAGGC |
|----|------|---------------------------------|--------------------|
|    | 2298 | GUGCCUAC CUGAUGA X GAA AGAAUAAU |                    |
|    | 2301 | GUCGUGCC CUGAUGA X GAA ACUAGAAU |                    |
|    | 2316 | AACAUGGC CUGAUGA X GAA AUCACCGU |                    |
| 5  | 2324 | GCCAGAAG CUGAUGA X GAA ACAUGGCA |                    |
|    | 2325 | AGCCAGAA CUGAUGA X GAA AACAUGGC | GCCAUGUUC UUCUGGCU |
|    | 2327 | GUAGCCAG CUGAUGA X GAA AGAACAUG | CAUGUUCUU CUGGCUAC |
|    | 2328 | AGUAGCCA CUGAUGA X GAA AAGAACAU | AUGUUCUUC UGGCUACU |
|    | 2334 | ACAAGAAG CUGAUGA X GAA AGCCAGAA | UUCUGGCUA CUUCUUGU |
| 10 | 2337 | AUGACAAG CUGAUGA X GAA AGUAGCCA | UGGCUACUU CUUGUCAU |
|    | 2338 | GAUGACAA CUGAUGA X GAA AAGUAGCC | GGCUACUUC UUGUCAUC |
|    | 2340 | AUGAUGAC CUGAUGA X GAA AGAAGUAG | CUACUUCUU GUCAUCAU |
|    | 2343 | AGGAUGAU CUGAUGA X GAA ACAAGAAG | CUUCUUGUC AUCAUCCU |
|    | 2346 | CCUAGGAU CUGAUGA X GAA AUGACAAG | CUUGUCAUC AUCCUAGG |
| 15 | 2349 | GUCCCUAG CUGAUGA X GAA AUGAUGAC | GUCAUCAUC CUAGGGAC |
|    | 2352 | ACGGUCCC CUGAUGA X GAA AGGAUGAU | AUCAUCCUA GGGACCGU |
|    | 2361 | GCCCGCUU CUGAUGA X GAA ACGGUCCC | GGGACCGUU AAGCGGGC |
|    | 2362 | GGCCCGCU CUGAUGA X GAA AACGGUCC | GGACCGUUA AGCGGGCC |
|    | 2396 | UGGACAAG CUGAUGA X GAA AGCCUGUC | GACAGGCUA CUUGUCCA |
| 20 | 2399 | CGAUGGAC CUGAUGA X GAA AGUAGCCU | AGGCUACUU GUCCAUCG |
|    | 2402 | UGACGAUG CUGAUGA X GAA ACAAGUAG | CUACUUGUC CAUCGUCA |
|    | 2406 | UCCAUGAC CUGAUGA X GAA AUGGACAA | UUGUCCAUC GUCAUGGA |
|    | 2409 | GGAUCCAU CUGAUGA X GAA ACGAUGGA | UCCAUCGUC AUGGAUCC |
|    | 2416 | UUCAUCUG CUGAUGA X GAA AUCCAUGA | UCAUGGAUC CAGAUGAA |
| 25 | 2427 | UCCAAUGG CUGAUGA X GAA AGUUCAUC | GAUGAACUC CCAUUGGA |
|    | 2432 | GUUCAUCC CUGAUGA X GAA AUGGGAGU | ACUCCCAUU GGAUGAAC |
|    | 2443 | UCGUUCAC CUGAUGA X GAA AUGUUCAU | AUGAACAUU GUGAACGA |
|    | 2458 | GGCAUCAU CUGAUGA X GAA AGGCAGUC | GACUGCCUU AUGAUGCC |
|    | 2459 | UGGCAUCA CUGAUGA X GAA AAGGCAGU | ACUGCCUUA UGAUGCCA |
| 30 | 2480 | CUCUGGGG CUGAUGA X GAA AUUCCCAU | AUGGGAAUU CCCCAGAG |
|    | 2481 | UCUCUGGG CUGAUGA X GAA AAUUCCCA | UGGGAAUUC CCCAGAGA |
|    | 2502 | GGCUUACC CUGAUGA X GAA AGGUUCAG | CUGAACCUA GGUAAGCC |
|    | 2506 | AAGAGGCU CUGAUGA X GAA ACCUAGGU | ACCUAGGUA AGCCUCUU |
|    |      |                                 |                    |

|    | 2512 | ACGGCCAA CUGAU  | SA X | GAA | AGGCUUAC | GUAAGCCUC UUGGCCGU |
|----|------|-----------------|------|-----|----------|--------------------|
|    | 2514 | CCACGGCC CUGAU  | GA X | GAA | AGAGGCUU | AAGCCUCUU GGCCGUGG |
|    | 2528 | CUUGGCCA CUGAUG | a x  | GAA | AGGCACCA | UGGUGCCUU UGGCCAAG |
|    | 2529 | UCUUGGCC CUGAUG | SA X | GAA | AAGGCACC | GGUGCCUUU GGCCAAGA |
| 5  | 2541 | UCUGCUUC CUGAUG | X AS | GAA | AUCUCUUG | CAAGAGAUU GAAGCAGA |
|    | 2555 | CAAUUCCA CUGAUG | a x  | GAA | AGGCAUCU | AGAUGCCUU UGGAAUUG |
|    | 2556 | UCAAUUCC CUGAUG | A X  | GAA | AAGGCAUC | GAUGCCUUU GGAAUUGA |
|    | 2562 | GUCUUGUC CUGAUG | A X  | GAA | AUUCCAAA | UUUGGAAUU GACAAGAC |
|    | 2578 | UGUCCUGC CUGAUG | A X  | GAA | AGUUGCUG | CAGCAACUU GCAGGACA |
| 10 | 2589 | UUGACUGC CUGAUG | A X  | GAA | ACUGUCCU | AGGACAGUA GCAGUCAA |
|    | 2595 | AACAUUUU CUGAUG | a x  | GAA | ACUGCUAC | GUAGCAGUC AAAAUGUU |
|    | 2603 | CUUCUUUC CUGAUG | a x  | GAA | ACAUUUUG | CAAAAUGUU GAAAGAAG |
|    | 2632 | GAGAGCUC CUGAUG | A X  | GAA | AUGCUCAC | GUGAGCAUC GAGCUCUC |
|    | 2638 | AGACAUGA CUGAUG | A X  | GAA | AGCUCGAU | AUCGAGCUC UCAUGUCU |
| 15 | 2640 | UCAGACAU CUGAUG | АX   | GAA | AGAGCUCG | CGAGCUCUC AUGUCUGA |
|    | 2645 | UGAGUUCA CUGAUG | A X  | GAA | ACAUGAGA | UCUCAUGUC UGARCUCA |
|    | 2652 | AGGAUCUU CUGAUG | АХ   | GAA | AGUUCAGA | UCUGAACUC AAGAUCCU |
|    | 2658 | UGAAUGAG CUGAUG | АХ   | GAA | AUCUUGAG | CUCAAGAUC CUCAUUCA |
|    | 2661 | AUAUGAAU CUGAUG | АХ   | GAA | AGGAUCUU | AAGAUCCUC AUUCAUAU |
| 20 | 2664 | CCAAUAUG CUGAUG | АХ   | GAA | AUGAGGAU | AUCCUCAUU CAUAUUGG |
|    | 2665 | ACCAAUAU CUGAUG | АХ   | GAA | AAUGAGGA | UCCUCAUUC AUAUUGGU |
|    | 2668 | GUGACCAA CUGAUG | АХ   | GAA | AUGAAUGA | UCAUUCAUA UUGGUCAC |
|    | 2670 | UGGUGACC CUGAUG | A X  | GAA | AUAUGAAU | AUUCAUAUU GGUCACCA |
|    | 2674 | GAGAUGGU CUGAUG | A X  | GAA | ACCAAUAU | AUAUUGGUC ACCAUCUC |
| 25 | 2680 | CACAUUGA CUGAUG | АХ   | GAA | AUGGUGAC | GUCACCAUC UCAAUGUG |
|    | 2682 | ACCACAUU CUGAUG | A X  | GAA | AGAUGGUG | CACCAUCUC AAUGUGGU |
|    | 2691 | AGAAGGUU CUGAUG | A X  | GAA | ACCACAUU | AAUGUGGUC AACCUUCU |
|    | 2697 | GCACCUAG CUGAUG | A X  | GAA | AGGUUGAC | GUCAACCUU CUAGGUGC |
|    | 2698 | GGCACCUA CUGAUG | A X  | GAA | AAGGUUGA | UCAACCUUC UAGGUGCC |
| 30 | 2700 | CAGGCACC CUGAUG | АХ   | GAA | AGAAGGUU | AACCUUCUA GGUGCCUG |
|    | 2710 | UGGCUUGG CUGAUG | АХ   | GAA | ACAGGCAC | GUGCCUGUA CCAAGCCA |
|    | 2730 | AUCACCAU CUGAUG | АХ   | GAA | AGUGGCCC | GGGCCACUC AUGGUGAU |
|    | 2739 | AAUUCCAC CUGAUG | ΑХ   | GAA | AUCACCAU | AUGGUGAUU GUGGAAUU |

|    | 2747 | AUUUGCAG CUGAUGA X GAA AUUCCACA  | UGUGGAAUU CUGCAAAU |
|----|------|----------------------------------|--------------------|
|    | 2748 | AAUUUGCA CUGAUGA X GAA AAUUCCAC  | GUGGAAUUC UGCAAAUU |
|    | 2756 | GGUUUCCA CUGAUGA X GAA AUUUGCAG  | CUGCAAAUU UGGAAACC |
|    | 2757 | AGGUUUCC CUGAUGA X GAA AAUUUGCA  | UGCAAAUUU GGAAACCU |
| 5  | 2768 | GGUAAGUG CUGAUGA X GAA ACAGGUUU  | AAACCUGUC CACUUACC |
|    | 2773 | CCUCAGGU CUGAUGA X GAA AGUGGACA  | UGUCCACUU ACCUGAGG |
|    | 2774 | UCCUCAGG CUGAUGA X GAA AAGUGGAC  | GUCCACUUA CCUGAGGA |
|    | 2798 | AGGGGACA CUGAUGA X GAA AUUCAUUU  | AAAUGAAUU UGUCCCCU |
|    | 2799 | UAGGGGAC CUGAUGA X GAA AAUUCAUU  | AAUGAAUUU GUCCCCUA |
| 10 | 2802 | UUGUAGGG CUGAUGA X GAA ACAAAUUC  | GAAUUUGUC CCCUACAA |
|    | 2807 | UGGUCUUG CUGAUGA X GAA AGGGGACA  | UGUCCCCUA CAAGACCA |
|    | 2828 | CUUGACGG CUGAUGA X GAA AUCGUGCC  | GGCACGAUU CCGUCAAG |
|    | 2829 | CCUUGACG CUGAUGA X GAA AAUCGUGC  | GCACGAUUC CGUCAAGG |
|    | 2833 | UUUCCCUU CUGAUGA X GAA ACGGAAUC  | GAUUCCGUC AAGGGAAA |
| 15 | 2846 | CUCCAACG CUGAUGA X GAA AGUCUUUC  | GAAAGACUA CGUUGGAG |
|    | 2850 | AUUGCUCC CUGAUGA X GAA ACGUAGUC  | GACUACGUU GGAGCAAU |
|    | 2859 | UCCACAGG CUGAUGA X GAA AUUGCUCC  | GGAGCAAUC CCUGUGGA |
|    | 2869 | CCGUUUCA CUGAUGA X GAA AUCCACAG  | CUGUGGAUC UGAAACGG |
|    | 2882 | UGCUGUCC CUGAUGA X GAA AGCGCCGU  | ACGGCGCUU GGACAGCA |
| 20 | 2892 | CUACUGGU CUGAUGA X GAA AUGCUGUC  | GACAGCAUC ACCAGUAG |
|    | 2899 | GCUCUGGC CUGAUGA X GAA ACUGGUGA  | UCACCAGUA GCCAGAGC |
|    | 2909 | AGCUGGCU CUGAUGA X GAA AGCUCUGG  | CCAGAGCUC AGCCAGCU |
|    | 2918 | CAAAUCCA CUGAUGA X GAA AGCUGGCU  | AGCCAGCUC UGGAUUUG |
|    | 2924 | CCUCCACA CUGALIGA X GAA AUCCAGAG | CUCUGGAUU UGUGGAGG |
| 25 | 2925 | UCCUCCAC CUGAUGA X GAA AAUCCAGA  | UCUGGAUUU GUGGAGGA |
|    | 2939 | CACUGAGG CUGAUGA X GAA ACUUCUCC  | GGAGAAGUC CCUCAGUG |
|    | 2943 | ACAUCACU CUGAUGA X GAA AGGGACUU  | AAGUCCCUC AGUGAUGU |
|    | 2952 | UCUUCUUC CUGAUGA X GAA ACAUCACU  | AGUGAUGUA GAAGAAGA |
|    | 2968 | AUCUUCAG CUGAUGA X GAA AGCUUCCU  | AGGAAGCUC CUGAAGAU |
| 30 | 2977 | CUUAUACA CUGAUGA X GAA AUCUUCAG  | CUGAAGAUC UGUAUAAG |
|    | 2981 | AGUCCUUA CUGAUGA X GAA ACAGAUCU  | AGAUCUGUA UAAGGACU |
|    | 2983 | GAAGUCCU CUGAUGA X GAA AUACAGAU  | AUCUGUAUA AGGACUUC |
|    | 2990 | AGGUCAGG CUGAUGA X GAA AGUCCUUA  | UAAGGACUU CCUGACCU |

|    | 2991 | AAGGUCAG | CUGAUGA | X | GAA | AAGUCCUU  | AAGGACUUC | CUGACCUU |
|----|------|----------|---------|---|-----|-----------|-----------|----------|
|    | 2999 | GAUGCUCC | CUGAUGA | X | GAA | AGGUCAGG  | CCUGACCUU | GGAGCAUC |
|    | 3007 | ACAGAUGA | CUGAUGA | X | GAA | AUGCUCCA  | UGGAGCAUC | UCAUCUGU |
|    | 3009 | UAACAGAU | CUGAUGA | X | GAA | AGAUGCUC  | GAGCAUCUC | AUCUGUUA |
| 5  | 3012 | CUGUAACA | CUGAUGA | X | GAA | AUGAGAUG  | CAUCUCAUC | UGUUACAG |
|    | 3016 | GAAGCUGU | CUGAUGA | X | GAA | ACAGAUGA  | UCAUCUGUU | ACAGCUUC |
|    | 3017 | GGAAGCUG | CUGAUGA | X | GAA | AACAGAUG  | CAUCUGUUA | CAGCUUCC |
|    | 3023 | CCACUUGG | CUGAUGA | x | GAA | AGCUGUAA  | UUACAGCUU | CCAAGUGG |
|    | 3024 | GCCACUUG | CUGAUGA | X | GAA | AAGCUGUA  | UACAGCUUC | CAAGUGGC |
| 10 | 3034 | CAUGCCCU | CUGAUGA | x | GAA | AGCCACUU  | AAGUGGCUA | AGGGCAUG |
|    | 3047 | AUGCCAAG | CUGAUGA | x | GAA | ACUCCAUG  | CAUGGAGUU | CUUGGCAU |
|    | 3048 | GAUGCCAA | CUGAUGA | x | GAA | AACUCCAU  | AUGGAGUUC | UUGGCAUC |
|    | 3050 | GCGAUGCC | CUGAUGA | x | GAA | AGAACUCC  | GGAGUUCUU | GGCAUCGC |
|    | 3056 | ACUUUCGC | CUGAUGA | x | GAA | AUGCCAAG  | CUUGGCAUC | GCGAAAGU |
| 15 | 3067 | CCUGUGGA | CUGAUGA | x | GAA | ACACUUUC  | GAAAGUGUA | UCCACAGG |
|    | 3069 | UCCCUGUG | CUGAUGA | x | GAA | AUACACUU  | AAGUGUAUC | CACAGGGA |
|    | 3094 | UAAGAGGA | CUGAUGA | X | GAA | AUUUCGUG  | CACGAAAUA | UCCUCUUA |
|    | 3096 | GAUAAGAG | CUGAUGA | X | GAA | AUAUUUCG  | CGAAAUAUC | CUCUUAUC |
|    | 3099 | UCCGAUAA | CUGAUGA | X | GAA | AGGAUAUU  | AAUAUCCUC | UUAUCGGA |
| 20 | 3101 | UCUCCGAU | CUGAUGA | X | GAA | AGAGGAUA  | UAUCCUCUU | AUCGGAGA |
|    | 3102 | UUCUCCGA | CUGAUGA | X | GAA | AAGAGGAU  | AUCCUCUUA | UCGGAGAA |
|    | 3104 | UCUUCUCC | CUGAUGA | X | GAA | AUAAGAGG  | CCUCUUAUC | GGAGAAGA |
|    | 3120 | CAGAUUUU | CUGAUGA | X | GAA | ACCACGUU  | AACGUGGUU | AAAAUCUG |
|    | 3121 | ACAGAUUU | CUGAUGA | X | GAA | AACCACGU  | ACGUGGUUA | AAAUCUGU |
| 25 | 3126 | AAGUCACA | CUGAUGA | X | GAA | AUUUUAAC  | GUUAAAAUC | UGUGACUU |
|    | 3134 | CCAAGCCA | CUGAUGA | X | GAA | AGUCACAG  | CUGUGACUU | UGGCUUGG |
|    | 3135 | GCCAAGCC | CUGAUGA | X | GAA | AAGUCACA  | UGUGACUUU | GGCUUGGC |
|    | 3140 | CCCGGGCC | CUGAUGA | X | GAA | AGCCAAAG  | CUUUGGCUU | GCCCGGG  |
|    | 3151 | UUUAUAAA | CUGAUGA | X | GAA | AUCCCGGG  | CCCGGGAUA | UUUAUAAA |
| 30 | 3153 | UCUUUAUA | CUGAUGA | X | GAA | AUAUCCCG  | CGGGAUAUU | UAUAAAGA |
|    | 3154 | AUCUUUAU | CUGAUGA | X | GAA | AAUAUCCC  | GGGAUAUUU | AUAAAGAU |
|    | 3155 | GAUCUUUA | CUGAUGA | X | GAA | AAAUAUCC  | GGAUAUUUA | UAAAGAUC |
|    | 3157 | UGGAUCUU | CUGAUGA | X | GAA | UAUAAAUAU | AUAUUUAUA | AAGAUCCA |
|    |      |          |         |   |     |           |           |          |

|    | 3163 | AUAAUCUG | CUGAUGA | X | GAA | AUCUUUAU | AUAAAGAUC | CAGAUUAU |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 3169 | UCUGACAU | CUGAUGA | X | GAA | AUCUGGAU | AUCCAGAUU | AUGUCAGA |
|    | 3170 | UUCUGACA | CUGAUGA | X | GAA | AAUCUGGA | UCCAGAUUA | UGUCAGAA |
|    | 3174 | ccuuuucu | CUGAUGA | X | GAA | ACAUAAUC | GAUUAUGUC | AGAAAAGG |
| 5  | 3190 | AGGGAGGC | CUGAUGA | X | GAA | AGCAUCUC | GAGAUGCUC | GCCUCCCU |
|    | 3195 | UUCAAAGG | CUGAUGA | X | GAA | AGGCGAGC | GCUCGCCUC | CCUUUGAA |
|    | 3199 | CCAUUUCA | CUGAUGA | X | GAA | AGGGAGGC | GCCUCCCUU | UGAAAUGG |
|    | 3200 | UCCAUUUC | CUGAUGA | X | GAA | AAGGGAGG | ccucccuuu | GAAAUGGA |
|    | 3225 | CUGUCAAA | CUGAUGA | x | GAA | AUUGUUUC | GAAACAAUU | UUUGACAG |
| 10 | 3226 | UCUGUCAA | CUGAUGA | x | GAA | AAUUGUUU | AAACAAUUU | UUGACAGA |
|    | 3227 | CUCUGUCA | CUGAUGA | x | GAA | AAAUUGUU | AACAAUUUU | UGACAGAG |
|    | 3228 | ACUCUGUC | CUGAUGA | X | GAA | AAAAUUGU | ACAAUUUUU | GACAGAGU |
|    | 3239 | GGAUUGUG | CUGAUGA | x | GAA | ACACUCUG | CAGAGUGUA | CACAAUCC |
|    | 3246 | UCACUCUG | CUGAUGA | x | GAA | AUUGUGUA | UACACAAUC | CAGAGUGA |
| 15 | 3258 | AAAGACCA | CUGAUGA | X | GAA | ACGUCACU | AGUGACGUC | UGGUCUUU |
|    | 3263 | CACCAAAA | CUGAUGA | x | GAA | ACCAGACG | CGUCUGGUC | UUUUGGUG |
|    | 3265 | AACACCAA | CUGAUGA | x | GAA | AGACCAGA | UCUGGUCUU | UUGGUGUU |
|    | 3266 | AAACACCA | CUGAUGA | x | GAA | AAGACCAG | CUGGUCUUU | UGGUGUUU |
|    | 3267 | AAAACACC | CUGAUGA | x | GAA | AAAGACCA | UGGUCUUUU | GGUGUUUU |
| 20 | 3273 | CACAGCAA | CUGAUGA | x | GAA | ACACCAAA | UUUGGUGUU | UUGCUGUG |
|    | 3274 | CCACAGCA | CUGAUGA | x | GAA | AACACCAA | UUGGUGUUU | UGCUGUGG |
|    | 3275 | CCCACAGC | CUGAUGA | x | GAA | AAACACCA | UGGUGUUUU | GCUGUGGG |
|    | 3288 | AAGGAAAA | CUGAUGA | x | GAA | AUUUCCCA | UGGGAAAUA | ບບບບດດວ  |
|    | 3290 | CUAAGGAA | CUGAUGA | x | GAA | AUAUUUCC | GGAAAUAUU | UUCCUUAG |
| 25 | 3291 | CCUAAGGA | CUGAUGA | x | GAA | AAUAUUUC | GAAAUAUUU | UCCUUAGG |
|    | 3292 | ACCUAAGG | CUGAUGA | X | GAA | UUUAUAAA | UUUUAUAAA | CCUUAGGU |
|    | 3293 | CACCUAAG | CUGAUGA | x | GAA | UUAUAAAA | AAUAUUUUC | CUUAGGUG |
|    | 3296 | AAGCACCU | CUGAUGA | x | GAA | AGGAAAAU | AUUUUCCUU | AGGUGCUU |
|    | 3297 | GAAGCACC | CUGAUGA | x | GAA | AAGGAAAA | UUUUCCUUA | GGUGCUUC |
| 30 | 3304 | AUAUGGAG | CUGAUGA | x | GAA | AGCACCUA | UAGGUGCUU | CUCCAUAU |
|    | 3305 | GAUAUGGA | CUGAUGA | x | GAA | AAGCACCU | AGGUGCUUC | UCCAUAUC |
|    | 3307 | AGGAUAUG | CUGAUGA | x | GAA | AGAAGCAC | GUGCUUCUC | CAUAUCCU |
|    | 3311 | CCCCAGGA | CUGAUGA | x | GAA | AUGGAGAA | UUCUCCAUA | UCCUGGGG |
|    |      |          |         |   |     |          |           |          |

PCT/US96/17480 WO 97/15662

|    | 3313 | UACCCCAG | CUGAUGA | X | GAA | AUAUGGAG | CUCCAUAUC | CUGGGGUA |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 3321 | UCAAUCUU | CUGAUGA | x | GAA | ACCCCAGG | CCUGGGGUA | AAGAUUGA |
|    | 3327 | UCUUCAUC | CUGAUGA | x | GAA | AUCUUUAC | GUAAAGAUU | GAUGAAGA |
|    | 3338 | GCCUACAA | CUGAUGA | x | GAA | AUUCUUCA | UGAAGAAUU | UUGUAGGC |
| 5  | 3339 | CGCCUACA | CUGAUGA | x | GAA | AAUUCUUC | GAAGAAUUU | UGUAGGCG |
|    | 3340 | UCGCCUAC | CUGAUGA | x | GAA | AAAUUCUU | AAGAAUUUU | GUAGGCGA |
|    | 3343 | CAAUCGCC | CUGAUGA | x | GAA | ACAAAAUU | AAUUUUGUA | GGCGAUUG |
|    | 3350 | CUUCUUUC | CUGAUGA | x | GAA | AUCGCCUA | UAGGCGAUU | GAAAGAAG |
|    | 3364 | CCUCAUUC | CUGAUGA | x | GAA | AGUUCCUU | AAGGAACUA | GAAUGAGG |
| 10 | 3382 | UGUAGUAU | CUGAUGA | x | GAA | AUCAGGGG | CCCCUGAUU | AUACUACA |
|    | 3383 | GUGUAGUA | CUGAUGA | x | GAA | AAUCAGGG | CCCUGAUUA | UACUACAC |
|    | 3385 | UGGUGUAG | CUGAUGA | x | GAA | AUAAUCAG | CUGAUUAUA | CUACACCA |
|    | 3388 | UUCUGGUG | CUGAUGA | x | GAA | AGUAUAAU | AUUAUACUA | CACCAGAA |
|    | 3401 | UGGUCUGG | CUGAUGA | x | GAA | ACAUUUCU | AGAAAUGUA | CCAGACCA |
| 15 | 3439 | GGGUCUCU | CUGAUGA | x | GAA | ACUGGGCU | AGCCCAGUC | AGAGACCC |
|    | 3452 | ACUCUGAA | CUGAUGA | x | GAA | ACGUGGGU | ACCCACGUU | UUCAGAGU |
|    | 3453 | AACUCUGA | CUGAUGA | x | GAA | AACGUGGG | CCCACGUUU | UCAGAGUU |
|    | 3454 | CAACUCUG | CUGAUGA | x | GAA | AAACGUGG | CCACGUUUU | CAGAGUUG |
|    | 3455 | CCAACUCU | CUGAUGA | x | GAA | AAAACGUG | CACGUUUUC | AGAGUUGG |
| 20 | 3461 | GUUCCACC | CUGAUGA | x | GAA | ACUCUGAA | UUCAGAGUU | GGUGGAAC |
|    | 3472 | AUUUCCCA | CUGAUGA | x | GAA | AUGUUCCA | UGGAACAUU | UGGGAAAU |
|    | 3473 | GAUUUCCC | CUGAUGA | X | GAA | AAUGUUCC | GGAACAUUU | GGGAAAUC |
|    | 3481 | UUGCAAGA | CUGAUGA | x | GAA | AUUUCCCA | UGGGAAAUC | UCUUGCAA |
|    | 3483 | GCUUGCAA | CUGAUGA | X | GAA | AGAUUUCC | GGAAAUCUC | UUGCAAGC |
| 25 | 3485 | UAGCUUGC | CUGAUGA | X | GAA | AGAGAUUU | AAAUCUCUU | GCAAGCUA |
|    | 3493 | CUGAGCAU | CUGAUGA | X | GAA | AGCUUGCA | UGCAAGCUA | AUGCUCAG |
|    | 3499 | AUCCUGCU | CUGAUGA | X | GAA | AGCAUUAG | CUAAUGCUC | AGCAGGAU |
|    | 3518 | GAACAAUG | CUGAUGA | X | GAA | AGUCUUUG | CAAAGACUA | CAUUGUUC |
|    | 3522 | GGAAGAAC | CUGAUGA | X | GAA | AUGUAGUC | GACUACAUU | GUUCUUCC |
| 30 | 3525 | AUCGGAAG | CUGAUGA | X | GAA | ACAAUGUA | UACAUUGUU | CUUCCGAU |
|    | 3526 | UAUCGGAA | CUGAUGA | X | GAA | AACAAUGU | ACAUUGUUC | UUCCGAUA |
|    | 3528 | GAUAUCGG | CUGAUGA | X | GAA | AGAACAAU | AUUGUUCUU | CCGAUAUC |
|    | 3529 | UGAUAUCG | CUGAUGA | x | GAA | AAGAACAA | UUGUUCUUC | CGAUAUCA |

|    | 3534 | GUCUCUGA | CUGAUGA | X | GAA | AUCGGAAG | CUUCCGAUA | UCAGAGAC |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 3536 | AAGUCUCU | CUGAUGA | x | GAA | AUAUCGGA | UCCGAUAUC | AGAGACUU |
|    | 3544 | CAUGCUCA | CUGAUGA | x | GAA | AGUCUCUG | CAGAGACUU | UGAGCAUG |
|    | 3545 | CCAUGCUC | CUGAUGA | X | GAA | AAGUCUCU | AGAGACUUU | GAGCAUGG |
| 5  | 3562 | GAGUCCAG | CUGAUGA | X | GAA | AUCCUCUU | AAGAGGAUU | CUGGACUC |
|    | 3563 | AGAGUCCA | CUGAUGA | x | GAA | AAUCCUCU | AGAGGAUUC | UGGACUCU |
|    | 3570 | GGCAGAGA | CUGAUGA | X | GAA | AGUCCAGA | UCUGGACUC | UCUCUGCC |
|    | 3572 | UAGGCAGA | CUGAUGA | X | GAA | AGAGUCCA | UGGACUCUC | UCUGCCUA |
|    | 3574 | GGUAGGCA | CUGAUGA | x | GAA | AGAGAGUC | GACUCUCUC | UGCCUACC |
| 10 | 3580 | AGGUGAGG | CUGAUGA | x | GAA | AGGCAGAG | CUCUGCCUA | CCUCACCU |
|    | 3584 | AAACAGGU | CUGAUGA | X | GAA | AGGUAGGC | GCCUACCUC | ACCUGUUU |
|    | 3591 | AUACAGGA | CUGAUGA | x | GAA | ACAGGUGA | UCACCUGUU | UCCUGUAU |
|    | 3592 | CAUACAGG | CUGAUGA | x | GAA | AACAGGUG | CACCUGUUU | CCUGUAUG |
|    | 3593 | CCAUACAG | CUGAUGA | x | GAA | AAACAGGU | ACCUGUUUC | CUGUAUGG |
| 15 | 3598 | CUCCUCCA | CUGAUGA | x | GAA | ACAGGAAA | UUUCCUGUA | UGGAGGAG |
|    | 3615 | GGGUCACA | CUGAUGA | x | GAA | ACUUCCUC | GAGGAAGUA | UGUGACCC |
|    | 3629 | CAUAAUGG | CUGAUGA | x | GAA | AUUUGGGG | CCCCAAAUU | CCAUUAUG |
|    | 3630 | UCAUAAUG | CUGAUGA | x | GAA | AAUUUGGG | CCCAAAUUC | CAUUAUGA |
|    | 3634 | GUUGUCAU | CUGAUGA | x | GAA | AUGGAAUU | AAUUCCAUU | AUGACAAC |
| 20 | 3635 | UGUUGUCA | CUGAUGA | X | GAA | AAUGGAAU | AUUCCAUUA | UGACAACA |
|    | 3654 | UACUGACU | CUGAUGA | x | GAA | AUUCCUGC | GCAGGAAUC | AGUCAGUA |
|    | 3658 | CAGAUACU | CUGAUGA | X | GAA | ACUGAUUC | GAAUCAGUC | AGUAUCUG |
|    | 3662 | UCUGCAGA | CUGAUGA | X | GAA | ACUGACUG | CAGUCAGUA | UCUGCAGA |
|    | 3664 | GUUCUGCA | CUGAUGA | X | GAA | AUACUGAC | GUCAGUAUC | UGCAGAAC |
| 25 | 3676 | CUUUCGCU | CUGAUGA | X | GAA | ACUGUUCU | AGAACAGUA | AGCGAAAG |
|    | 3702 | AAUGUUUU | CUGAUGA | X | GAA | ACACUCAC | GUGAGUGUA | AAAACAUU |
|    | 3710 | UAUCUUCA |         |   |     |          | AAAAACAUU | UGAAGAUA |
|    | 3711 | AUAUCUUC | CUGAUGA | X | GAA | AAUGUUUU | AAAACAUUU | GAAGAUAU |
|    | 3718 | UAACGGGA | CUGAUGA | X | GAA | AUCUUCAA | UUGAAGAUA | UCCCGUUA |
| 30 | 3720 |          |         |   |     | AUAUCUUC | GAAGAUAUC | CCGUUAGA |
|    | 3725 | GUUCUUCU | CUGAUGA | x | GAA | ACGGGAUA | UAUCCCGUU | AGAAGAAC |
|    | 3726 | GGUUCUUC | CUGAUGA | X | GAA | AACGGGAU | AUCCCGUUA | GAAGAACC |
|    | 3741 | AUUACUUU | CUGAUGA | x | GAA | ACUUCUGG | CCAGAAGUA | AAAGUAAU |

|    | 3747 | UCUGGGAU | CUGAUGA | x | GAA | ACUUUUAC | GUAAAAGUA | AUCCCAGA |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 3750 | UCAUCUGG | CUGAUGA | x | GAA | AUUACUUU | AAAGUAAUC | CCAGAUGA |
|    | 3778 | AAGAACCA | CUGAUGA | x | GAA | ACCACUGU | ACAGUGGUA | UGGUUCUU |
|    | 3783 | GAGGCAAG | CUGAUGA | x | GAA | ACCAUACC | GGUAUGGUU | CUUGCCUC |
| 5  | 3784 | UGAGGCAA | CUGAUGA | x | GAA | AACCAUAC | GUAUGGUUC | UUGCCUCA |
|    | 3786 | UCUGAGGC | CUGAUGA | x | GAA | AGAACCAU | AUGGUUCUU | GCCUCAGA |
|    | 3791 | GCUCUUCU | CUGAUGA | x | GAA | AGGCAAGA | UCUUGCCUC | AGAAGAGC |
|    | 3808 | GUCUUCCA | CUGAUGA | X | GAA | AGUUUUCA | UGAAAACUU | UGGAAGAC |
|    | 3809 | UGUCUUCC | CUGAUGA | x | GAA | AAGUUUUC | GAAAACUUU | GGAAGACA |
| 10 | 3827 | AUGGAGAU | CUGAUGA | X | GAA | AUUUGGUU | AACCAAAUU | AUCUCCAU |
|    | 3828 | GAUGGAGA | CUGAUGA | X | GAA | AAUUUGGU | ACCAAAUUA | UCUCCAUC |
|    | 3830 | AAGAUGGA | CUGAUGA | x | GAA | AUAAUUUG | CAAAUUAUC | UCCAUCUU |
|    | 3832 | AAAAGAUG | CUGAUGA | x | GAA | AGAUAAUU | AAUUAUCUC | CAUCUUUU |
|    | 3836 | CACCAAAA | CUGAUGA | X | GAA | AUGGAGAU | AUCUCCAUC | UUUUGGUG |
| 15 | 3838 | UCCACCÃA | CUGAUGA | x | GAA | AGAUGGAG | CUCCAUCUU | UUGGUGGA |
|    | 3839 | UUCCACCA | CUGAUGA | x | GAA | AAGAUGGA | UCCAUCUUU | UGGUGGAA |
|    | 3840 | AUUCCACC | CUGAUGA | X | GAA | AAAGAUGG | CCAUCUUUU | GGUGGAAU |
|    | 3872 | AUGCCACA | CUGAUGA | X | GAA | ACUCCCUG | CAGGGAGUC | UGUGGCAU |
|    | 3881 | AGCCUUCA | CUGAUGA | X | GAA | AUGCCACA | UGUGGCAUC | UGAAGGCU |
| 20 | 3890 | UCUGGUUU | CUGAUGA | X | GAA | AGCCUUCA | UGAAGGCUC | AAACCAGA |
|    | 3908 | CGGACUGG | CUGAUGA | X | GAA | AGCCGCUU | AAGCGGCUA | CCAGUCCG |
|    | 3914 | GAUAUCCG | CUGAUGA | x | GAA | ACUGGUAG | CUACCAGUC | CGGAUAUC |
|    | 3920 | CGGAGUGA | CUGAUGA | X | GAA | AUCCGGAC | GUCCGGAUA | UCACUCCG |
|    | 3922 | AUCGGAGU | CUGAUGA | X | GAA | AUAUCCGG | CCGGAUAUC | ACUCCGAU |
| 25 | 3926 | UGUCAUCG | CUGAUGA | X | GAA | AGUGAUAU | AUAUCACUC | CGAUGACA |
|    | 3950 | CACUGGAG | CUGAUGA | X | GAA | ACACGGUG | CACCGUGUA | CUCCAGUG |
|    | 3953 | CCUCACUG | CUGAUGA | X | GAA | AGUACACG | CGUGUACUC | CAGUGAGG |
|    | 3972 | AGCUUUAA | CUGAUGA | X | GAA | AGUUCUGC | GCAGAACUU | UUAAAGCU |
|    | 3973 | CAGCUUUA | CUGAUGA | X | GAA | AAGUUCUG | CAGAACUUU | UAAAGCUG |
| 30 | 3974 | UCAGCUUU | CUGAUGA | x | GAA | AAAGUUCU | AGAACUUUU | AAAGCUGA |
| -  | 3975 | AUCAGCUU | CUGAUGA | X | GAA | AAAAGUUC | GAACUUUUA | AAGCUGAU |
|    | 3984 | CCAAUCUC | CUGAUGA | x | GAA | AUCAGCUU | AAGCUGAUA | GAGAUUGG |
|    | 3990 | UGCACUCC | CUGAUGA | x | GAA | AUCUCUAU | AUAGAGAUU | GGAGUGCA |

|    | 4006 | GGCUGUGC | CUGAUGA | X | GAA | ACCGGUUU | AAACCGGUA | GCACAGCC |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 4020 | GGCUGGAG | CUGAUGA | X | GAA | AUCUGGGC | GCCCAGAUU | CUCCAGCC |
|    | 4021 | AGGCUGGA | CUGAUGA | X | GAA | AAUCUGGG | CCCAGAUUC | UCCAGCCU |
|    | 4023 | UCAGGCUG | CUGAUGA | X | GAA | AGAAUCUG | CAGAUUCUC | CAGCCUGA |
| 5  | 4052 | CAGGAGGA | CUGAUGA | X | GAA | AGCUCAGU | ACUGAGCUC | UCCUCCUG |
|    | 4054 | AACAGGAG | CUGAUGA | X | GAA | AGAGCUCA | UGAGCUCUC | CUCCUGUU |
|    | 4057 | UUAAACAG | CUGAUGA | X | GAA | AGGAGAGC | GCUCUCCUC | CUGUUUAA |
|    | 4062 | UCCUUUUA | CUGAUGA | X | GAA | ACAGGAGG | CCUCCUGUU | UAAAAGGA |
|    | 4063 | nnccnnn  | CUGAUGA | X | GAA | AACAGGAG | CUCCUGUUU | AAAAGGAA |
| 10 | 4064 | CUUCCUUU | CUGAUGA | X | GAA | AAACAGGA | UCCUGUUUA | AAAGGAAG |
|    | 4076 | GGGGUGUG | CUGAUGA | X | GAA | AUGCUUCC | GGAAGCAUC | CACACCCC |
|    | 4089 | AUGUCCGG | CUGAUGA | X | GAA | AGUUGGGG | CCCCAACUC | CCGGACAU |
|    | 4098 | UCUCAUGU | CUGAUGA | x | GAA | AUGUCCGG | CCGGACAUC | ACAUGAGA |
|    | 4110 | UCUGAGCA | CUGAUGA | X | GAA | ACCUCUCA | UGAGAGGUC | UGCUCAGA |
| 15 | 4115 | CAAAAUCU | CUGAUGA | X | GAA | AGCAGACC | GGUCUGCUC | AGAUUUUG |
|    | 4120 | CACUUCAA | CUGAUGA | X | GAA | AUCUGAGC | GCUCAGAUU | UUGAAGUG |
|    | 4121 | ACACUUCA | CUGAUGA | x | GAA | AAUCUGAG | CUCAGAUUU | UGAAGUGU |
|    | 4122 | AACACUUC | CUGAUGA | x | GAA | AAAUCUGA | UCAGAUUUU | GAAGUGUU |
|    | 4130 | GAAAGAAC | CUGAUGA | X | GAA | ACACUUCA | UGAAGUGUU | GUUCUUUC |
| 20 | 4133 | GUGGAAAG | CUGAUGA | x | GAA | ACAACACU | AGUGUUGUU | CUUUCCAC |
|    | 4134 | GGUGGAAA | CUGAUGA | X | GAA | AACAACAC | GUGUUGUUC | UUUCCACC |
|    | 4136 | CUGGUGGA | CUGAUGA | X | GAA | AGAACAAC | GUUGUUCUU | UCCACCAG |
|    | 4137 | GCUGGUGG | CUGAUGA | X | GAA | AAGAACAA | UUGUUCUUU | CCACCAGC |
|    | 4138 | UGCUGGUG | CUGAUGA | X | GAA | AAAGAACA | UGUUCUUUC | CACCAGCA |
| 25 | 4153 | AAUGCGGC | CUGAUGA | X | GAA | ACUUCCUG | CAGGAAGUA | GCCGCAUU |
|    | 4161 | GAAAAUCA | CUGAUGA | x | GAA | AUGCGGCU | AGCCGCAUU | UGAUUUUC |
|    | 4162 | UGAAAAUC | CUGAUGA | X | GAA | AAUGCGGC | GCCGCAUUU | GAUUUUCA |
|    | 4166 | GAAAUGAA | CUGAUGA | X | GAA | AUCAAAUG | CAUUUGAUU | UUCAUUUC |
|    | 4167 | CGAAAUGA | CUGAUGA | X | GAA | AAUCAAAU | AUUUGAUUU | UCAUUUCG |
| 30 | 4168 | UCGAAAUG | CUGAUGA | X | GAA | AAAUCAAA | UUUGAUUUU | CAUUUCGA |
|    | 4169 | GUCGAAAU | CUGAUGA | x | GAA | AAAAUCAA | UUGAUUUUC | AUUUCGAC |
|    | 4172 | GUUGUCGA | CUGAUGA | x | GAA | AUGAAAAU | AUUUUCAUU | UCGACAAC |
|    | 4173 | UGUUGUCG | CUGAUGA | x | GAA | AAUGAAAA | UUUUCAUUU | CGACAACA |

117

|   | 4174 | CUGUUGUC | CUGAUGA | X | GAA | AAAUGAAA | UUUCAUUUC | GACAACAG |
|---|------|----------|---------|---|-----|----------|-----------|----------|
|   | 4194 | UGCAGUCC | CUGAUGA | X | GAA | AGGUCCUU | AAGGACCUC | GGACUGCA |
|   | 4214 | GCCUAGAA | CUGAUGA | X | GAA | AGCUGGCU | AGCCAGCUC | UUCUAGGC |
|   | 4216 | AAGCCUAG | CUGAUGA | X | GAA | AGAGCUGG | CCAGCUCUU | CUAGGCUU |
| 5 | 4217 | CAAGCCUA | CUGAUGA | X | GAA | AAGAGCUG | CAGCUCUUC | UAGGCUUG |
|   | 4219 | CACAAGCC | CUGAUGA | x | GAA | AGAAGAGC | GCUCUUCUA | GCCUUGUG |

Where "X" represents stem II region of a HH ribozyme (Hertel et al., 1992 Nucleic Acids Res. 20 3252). The length of stem II may be  $\geq$  2 base-pairs.

Table V: Human KDR VEGF Receptor-Hairpin Ribozyme and Substrate Sequences

|    | nt.      |          |      | Ha     | Hairnin Ribozyme Segmense                                 |                        |
|----|----------|----------|------|--------|---|------------------------|
|    | Position | ď        |      |        | ));;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;;                    | Substrate              |
|    | 11       | CGACGGCC | AGAA | GCACCU | CGACGGCC AGAA GCACCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGGUGCU GCU GGCCGIICG  |
| Ŋ  | 18       | CACAGGGC | AGAA | GCCAGC | CACAGGGC AGAA GCCAGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA  | Scheece are scenes     |
|    | 51       | CCCACAGA | AGAA | ອຍລວລອ | CCCACAGA AGAA GCCCGG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA  | SESSES SES SESSESSES   |
|    | 98       | UGAGCCUG | AGAA | GAUCAA | UGAGCCUG AGAA GAUCAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UUGAUCU GCC CAGGCUCA   |
|    | 318      | GAGGCCAA | AGAA | GUUUCC | GAGGCCAA AGAA GUUUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGAAACU GAC UUGGCCUC   |
|    | 358      | AAAUGGAG | AGAA | GUAAUC | AAAUGGAG AGAA GUAAUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAUUACA GAU CUCCAIIIII |
| 10 | 510      | CUGUUACC | AGAA | GGAACA | CUGUUACC AGAA GGAACA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UGUUCCU GAU GGUAACAG   |
|    | 623      | ACAUAAUA | AGAA | GGUAAC | ACAUAAUA AGAA GGUAAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GUUACCA GUC UAUUAUGU   |
|    | 683      | UUCCAUGA | AGAA | GACUCA | UUCCAUGA AGAA GACUCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UGAGUCC GUC UCAUGGAA   |
|    | 705      | ununcucc | AGAA | GAUAGU | UUUUCUCC AGAA GAUAGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | ACUAUCU GIII GGAGAAAA  |
|    | 833      | CACUCCCA | AGAA | GGGUUU | CACUCCCA AGAA GGGUUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AAACCCA GUC UGGGAGIIG  |
| 15 | 932      | ນດນນອອນຕ | AGAA | GCCCAC | UCUUGGUC AGAA GCCCAC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA  | GUGGGCU GAU GACCAAGA   |
|    | 1142     | CCAUAAUC | AGAA | GUACAU | CCAUAAUC AGAA GUACAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AUGUACU GAC GAUUAUGG   |
|    | 1259     | UCUCACCA | AGAA | GGGGUG | UCUCACCA AGAA GGGGUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CACCCCA GAU UGGUGAGA   |
|    | 1332     | AUGGCAUA | AGAA | GUACAU | AUGGCAUA AGAA GUACAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AUGUACG GUC UAUGCCAII  |

GCU CUGGAUUU

ACUUCCU GAC CUUGGAGC

GCUCCAAG AGAA GGAAGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA

2993

119 UCAGGCA GCU CACAGUCC GCUCACA GUC CUAGAGCG UVAUGAUG GAGACCG GCU GAACCUAG UGAAGCA GAU GCCUUUGG CACUUACC CCAAGCU GUC UCAGUGAC GCU UUGUACAA ACAUGCA GCC CACUGAGC GCCCACA GCC UCUGCCAA CACACCU GUU UGCAAGAA UAUGUCU GCC UUGCUCAA GAC GACAAGUA CUCCACA GAU CAUGUGGU GGAUCCA GAU GAACUCCC AUUGGCA GUU GGAGGAAG GCAGACA GAU CUACGUUU GUC AACGACU GCC UGUGUCA AGAAUCA GAAACCU UCAGCCA AAAUCCAG AGAA GGCUGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA SCUCAGUG AGAA GCAUGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA JUGAGCAA AGAA GACAUA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCCUGA ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA CGCUCUAG AGAA GUGAGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA JACUUGUC AGAA GAUUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA ACCACAUG AGAA GUGGAG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CAUCAUAA AGAA GUCGUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUAGGUUC AGAA GGUCUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCAAAGGC AGAA GCUUCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGUAAGUG AGAA GGUUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUUCCUCC AGAA GCCAAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA SUCACUGA AGAA GCUUGG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GACACA ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GUCUGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GUGGGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA UNCUUGCA AGAA GGUGUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA 36GAGUUC AGAA GGAUCC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA UUGUACAA AGAA AAACGUAG AGAA JUGGCAGA AGAA GGACUGUG AGAA 2418 1376 1413 1760 1918 2084 2492 2547 2765 2914 1569 1673 1717 1797 1967 1974 2021 2453

10

വ

GACCUCG GAC UGCAGGGA

UCCCUGCA AGAA GAGGUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA

4195

120

UGUUACA GCU UCCAAGUG AGAUCCA GAU UAUGUCAG GGCCCCU GAU UAUACUAC UGUACCA GAC CAUGCUGG CUGGACU GCU GGCACGGG CUCACCU GUU UCCUGUAU AAUCCCA GAU GACAACCA UCACUCC GAU GACACAGA UCUCUCU GCC UACCUCAC AGAGCCG GCC UGUGAGUG ACAACCA GAC GGACAGUG GCUACCA GUC CGGAUAUC CAGCCCA GAU UCUCCAGC GCC UGACACGG UAGCACA GCC CAGAUUCU UCCUCCU GUU UAAAAGGA GAGGUCU GCU CAGAUUUU CUGCUCA GAU UUUGAAGU UUCUCCA CACUUGGA AGAA GUAACA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGAUCU ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GUAGUAUA AGAA GGGGCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GGUACA ACCAGAGAAACACGCGUGGGGGGACAUUACCUGGUA CCCGUGCC AGAA GUCCAG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GUGAGGUA AGAA GAGAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGUGAG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA CACUCACA AGAA GGCUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGUUGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAUAUCCG AGAA GGUAGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UGGUUGUC AGAA GGGAUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCUGUGUC AGAA GAGUGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GUGCUA ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GCUGGAGA AGAA GGGCUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCGUGUCA AGAA GGAGAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGAGGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AAAAUCUG AGAA GACCUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAGCAG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA CUGACAUA AGAA CCAGCAUG AGAA AUACAGGA AGAA CACUGUCC AGAA UCCUUUUA AGAA ACUUCAAA AGAA AGAAUCUG AGAA 3019 3165 3378 3418 3575 3588 4016 4059 4116 3404 3689 4025 3753 3764 3911 3927 4011 4111 ហ 10 15

GGAGCCA GCU CUUCUAGG

121

CCUAGAAG AGAA GGCUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA

121

122

PCT/US96/17480

## Table VI: Mouse flk-1 VEGF Receptor-Hammerhead Ribozyme and Substrate Sequence

|    | nt   |               | bozyme S | sequence     | Substrate          |
|----|------|---------------|----------|--------------|--------------------|
| _  | Pos  | <del></del>   |          |              |                    |
| 5  | tio  | on            |          |              |                    |
|    | 13   | CCGUACCC CUG  | AUGA X C | GAA AUUCGCCC | GGGCGAAUU GGGUACGG |
|    | 18   | GGGUCCCG CUG  | AUGA X C | SAA ACCCAAUU | AAUUGGGUA CGGGACCC |
|    | 31   | UCGACCUC CUG  | AUGA X G | GAA AGGGGGGU | ACCCCCCUC GAGGUCGA |
|    | 37   | AUACCGUC CUG  | AUGA X G | AA ACCUCGAG  | CUCGAGGUC GACGGUAU |
| 10 | 44   | CUUAUCGA CUG  | AUGA X G | AA ACCGUCGA  | UCGACGGUA UCGAUAAG |
|    | 46   | AGCUUAUC CUG  | AUGA X G | AA AUACCGUC  | GACGGUAUC GAUAAGCU |
|    | 50   | AUCAAGCU CUG  | AUGA X G | AA AUCGAUAC  | GUAUCGAUA AGCUUGAU |
|    | 55   | UCGAUAUC CUG  | AUGA X G | AA AGCUUAUC  | GAUAAGCUU GAUAUCGA |
|    | 59   | GAAUUCGA CUG  | AUGA X G | AA AUCAAGCU  | AGCUUGAUA UCGAAUUC |
| 15 | - 61 | CCGAAUUC CUGA | AUGA X G | AA AUAUCAAG  | CUUGAUAUC GAAUUCGG |
|    | 66   | UGGGCCCG CUG  | UGA X G  | AA AUUCGAUA  | UAUCGAAUU CGGGCCCA |
|    | 67   | CUGGGCCC CUGA | LUGA X G | AA AAUUCGAU  | AUCGAAUUC GGGCCCAG |
|    | 83   | GGCUGCGG CUGA | uga x g  | AA ACACAGUC  | GACUGUGUC CCGCAGCC |
|    | 97   | AGCCAGGU CUGA | UGA X G  | AA AUCCCGGC  | GCCGGGAUA ACCUGGCU |
| 20 | 114  | GUCCGCGG CUGA | UGA X GA | AA AUCGGGUC  | GACCCGAUU CCGCGGAC |
|    | 115  | UGUCCGCG CUGA | UGA X GA | AA AAUCGGGU  | ACCCGAUUC CGCGGACA |
|    | 169  | ACCGGGGA CUGA | UGA X GA | AA AGCGCGGG  | cccgcgcuc uccccggu |
|    | 171  | AGACCGGG CUGA | UGA X GA | AA AGAGCGCG  | CGCGCUCUC CCCGGUCU |
|    | 178  | CAGCGCAA CUGA | UGA X GA | A ACCGGGGA   | UCCCCGGUC UUGCGCUG |
| 25 | 180  | CGCAGCGC CUGA | UGA X GA | A AGACCGGG   | CCCGGUCUU GCGCUGCG |
|    | 197  | AGAGGCGG CUGA | UGA X GA | A AUGGCCCC   | GGGGCCAUA CCGCCUCU |
|    | 204  | AAGUCACA CUGA | uga x ga | A AGGCGGUA   | UACCGCCUC UGUGACUU |
|    | 212  | CCGCAAAG CUGA | UGA X GA | A AGUCACAG   | CUGUGACUU CUUUGCGG |
|    | 213  | CCCGCAAA CUGA | UGA X GA | A AAGUCACA   | UGUGACUUC UUUGCGGG |
| 30 | 215  | GGCCCGCA CUGA | UGA X GA | A AGAAGUCA   | UGACUUCUU UGCGGGCC |

PCT/US96/17480 WO 97/15662

|    | 216 | UGGCCCGC | CUGAUGA | X | GAA | AAGAAGUC | GACUUCUUU | GCGGGCCA |
|----|-----|----------|---------|---|-----|----------|-----------|----------|
|    | 241 | CAGGCACA | CUGAUGA | X | GAA | ACUCCUUC | GAAGGAGUC | UGUGCCUG |
|    | 262 | UGGGCACA | CUGAUGA | X | GAA | AGCCCAGU | ACUGGGCUC | UGUGCCCA |
|    | 306 | GCGACAGC | CUGAUGA | X | GAA | AGCAGCGC | GCGCUGCUA | GCUGUCGC |
| 5  | 312 | CACAGAGC | CUGAUGA | X | GAA | ACAGCUAG | CUAGCUGUC | GCUCUGUG |
|    | 316 | GAACCACA | CUGAUGA | x | GAA | AGCGACAG | CUGUCGCUC | ugugguuc |
|    | 323 | CCACGCAG | CUGAUGA | x | GAA | ACCACAGA | ucugugguu | CUGCGUGG |
|    | 324 | UCCACGCA | CUGAUGA | x | GAA | AACCACAG | CUGUGGUUC | UGCGUGGA |
|    | 347 | AACCCACA | CUGAUGA | x | GAA | AGGCGGCU | AGCCGCCUC | UGUGGGUU |
| 10 | 355 | GCCAGUCA | CUGAUGA | x | GAA | ACCCACAG | CUGUGGGUU | UGACUGGC |
|    | 356 | CGCCAGUC | CUGAUGA | x | GAA | AACCCACA | UGUGGGUUU | GACUGGCG |
|    | 367 | AUGGAGAA | CUGAUGA | x | GAA | AUCGCCAG | CUGGCGAUU | UUCUCCAU |
|    | 368 | GAUGGAGA | CUGAUGA | x | GAA | AAUCGCCA | UGGCGAUUU | UCUCCAUC |
|    | 369 | GGAUGGAG | CUGAUGA | x | GAA | AAAUCGCC | GGCGAUUUU | CUCCAUCC |
| 15 | 370 | GGGAUGGA | CUGAUGA | x | GAA | AAAAUCGC | GCGAUUUUC | UCCAUCCC |
|    | 372 | GGGGGAUG | CUGAUGA | x | GAA | AGAAAAUC | GAUUUUCUC | CAUCCCCC |
|    | 376 | CUUGGGGG | CUGAUGA | x | GAA | AUGGAGAA | UUCUCCAUC | CCCCCAAG |
|    | 387 | UGUGUGCU | CUGAUGA | x | GAA | AGCUUGGG | CCCAAGCUC | AGCACACA |
|    | 405 | AUUGUCAG | CUGAUGA | x | GAA | AUGUCUUU | AAAGACAUA | CUGACAAU |
| 20 | 414 | UUUGCCAA | CUGAUGA | x | GAA | AUUGUCAG | CUGACAAUU | UUGGCAAA |
|    | 415 | AUUUGCCA | CUGAUGA | x | GAA | AAUUGUCA | UGACAAUUU | UGGCAAAU |
|    | 416 | UAUUUGCC | CUGAUGA | X | GAA | AAAUUGUC | GACAAUUUU | GGCAAAUA |
|    | 424 | AAGGGUUG | CUGAUGA | x | GAA | AUUUGCCA | UGGCAAAUA | CAACCCUU |
|    | 432 | GUAAUCUG | CUGAUGA | X | GAA | AGGGUUGU | ACAACCCUU | CAGAUUAC |
| 25 | 433 | AGUAAUCU | CUGAUGA | x | GAA | AAGGGUUG | CAACCCUUC | AGAUUACU |
|    | 438 | CUGCAAGU | CUGAUGA | X | GAA | AUCUGAAG | CUUCAGAUU | ACUUGCAG |
| •  | 439 | CCUGCAAG | CUGAUGA | x | GAA | AAUCUGAA | UUCAGAUUA | CUUGCAGG |
|    | 442 | UCCCCUGC | CUGAUGA | X | GAA | AGUAAUCU | AGAUUACUU | GCAGGGGA |
|    | 471 | UUGGGCCA | CUGAUGA | X | GAA | AGCCAGUC | GACUGGCUU | UGGCCCAA |
| 30 | 472 | AUUGGGCC | CUGAUGA | x | GAA | AAGCCAGU | ACUGGCUUU | GGCCCAAU |

|    | 484         | AUCACGCU CUGAUGA |   | ( GA | A AGCAUUGG | CCAAUGCUC AGCGUGAU |
|----|-------------|------------------|---|------|------------|--------------------|
|    | 493         | UUCCUCAG CUGAUGA |   |      |            |                    |
|    | 494         | UUUCCUCA CUGAUGA |   |      |            | THE COUNTY COUNTY  |
|    | 507         | GUCACCAA CUGAUGA |   |      |            |                    |
| 5  | 509         |                  |   |      |            | GAAAGGGUA UUGGUGAC |
| ,  |             | CAGUCACC CUGAUGA |   |      |            | AAGGGUAUU GGUGACUG |
|    | 538         | GCAGAAGA CUGAUGA |   |      |            | GUGACAGUA UCUUCUGC |
|    | 540         | UUGCAGAA CUGAUGA |   |      |            | GACAGUAUC UUCUGCAA |
|    | 542         | UUUUGCAG CUGAUGA |   |      |            | CAGUAUCUU CUGCAAAA |
|    | 543         | GUUUUGCA CUGAUGA |   |      |            | AGUAUCUUC UGCAAAAC |
| 10 | 555         | GGAAUGGU CUGAUGA | X | GAA  | AGUGUUUU   | AAAACACUC ACCAUUCC |
|    | 561         | ACCCUGGG CUGAUGA | X | GAA  | AUGGUGAG   | CUCACCAUU CCCAGGGU |
|    | 562         | CACCCUGG CUGAUGA | X | GAA  | AAUGGUGA   | UCACCAUUC CCAGGGUG |
|    | 573         | UCAUUUCC CUGAUGA | X | GAA  | ACCACCCU   | AGGGUGGUU GGAAAUGA |
|    | 583         | GGCUCCAG CUGAUGA | X | GAA  | AUCAUUUC   | GAAAUGAUA CUGGAGCC |
| 15 | 593         | AGCACUUG CUGAUGA | x | GAA  | AGGCUCCA   | UGGAGCCUA CAAGUGCU |
|    | 602         | CCCGGUAC CUGAUGA | x | GAA  | AGCACUUG   | CAAGUGCUC GUACCGGG |
|    | 605         | CGUCCCGG CUGAUGA | x | GAA  | ACGAGCAC   | GUGCUCGUA CCGGGACG |
|    | 615         | GCUAUGUC CUGAUGA | x | GAA  | ACGUCCCG   | CGGGACGUC GACAUAGC |
|    | 621         | GUGGAGGC CUGAUGA | x | GAA  | AUGUCGAC   | GUCGACAUA GCCUCCAC |
| 20 | <b>62</b> 6 | AAACAGUG CUGAUGA | x | GAA  | AGGCUAUG   | CAUAGCCUC CACUGUUU |
|    | 633         | UAGACAUA CUGAUGA | x | GAA  | ACAGUGGA   | UCCACUGUU UAUGUCUA |
|    | 634         | AUAGACAU CUGAUGA | x | GAA  | AACAGUGG   | CCACUGUUU AUGUCUAU |
|    | 635         | CAUAGACA CUGAUGA | х | GAA  | AAACAGUG   | CACUGUUUA UGUCUAUG |
|    | 639         | CGAACAUA CUGAUGA | x | GAA  | ACAUAAAC   | GUUUAUGUC UAUGUUCG |
| 25 | 641         | CUCGAACA CUGAUGA | х | GAA  | AGACAUAA   | UUAUGUCUA UGUUCGAG |
|    | 645         | UAAUCUCG CUGAUGA | x | GAA  | ACAUAGAC   | GUCUAUGUU CGAGAUUA |
|    | 646         |                  |   |      |            | UCUAUGUUC GAGAUUAC |
|    | 652         |                  |   |      |            | UUCGAGAUU ACAGAUCA |
|    | 653         |                  |   |      |            | UCGAGAUUA CAGAUCAC |
| 30 | 659         | UGAAUGGU CUGAUGA |   |      |            |                    |
|    | -           | COUNCIA ,        |   | JAM  | AMUDUUUAA  | UUACAGAUC ACCAUUCA |

PCT/US96/17480

WO 97/15662

|             |   | C00210021   | . ^   | GAA   | AUGUUAU  | AUCACCAUU CAUCGCCU  |
|-------------|---|---|---|---|--|---|
| 666         | GAGGCGAU  | CUGAUGA   | X   | GAA   | AAUGGUGA   | UCACCAUUC AUCGCCUC  |
| 669         | ACAGAGGC  | CUGAUGA   | X   | GAA   | AUGAAUGG   | CCAUUCAUC GCCUCUGU  |
| 674         | CACUGACA  | CUGAUGA   | x   | GAA   | AGGCGAUG   | CAUCGCCUC UGUCAGUG  |
| 678         | UGGUCACU  | CUGAUGA   | х   | GAA   | ACAGAGGC   | GCCUCUGUC AGUGACCA  |
| 696         | AUGUACAC  | CUGAUGA   | X   | GAA   | AUGCCAUG   | CAUGGCAUC GUGUACAU  |
| 701         | CGGUGAUG  | CUGAUGA   | x   | GAA   | ACACGAUG   | CAUCGUGUA CAUCACCG  |
| 705         | UUCUCGGU  | CUGAUGA   | x   | GAA   | AUGUACAC   | GUGUACAUC ACCGAGAA  |
| 735         | CGGCAGGG  | CUGAUGA   | x   | GAA   | AUCACCAC   | GUGGUGAUC CCCUGCCG  |
| 749         | UUGAAAUC  | CUGAUGA   | x   | GAA   | ACCCUCGG   | CCGAGGGUC GAUUUCAA  |
| 753         | AGGUUUGA  | CUGAUGA   | x   | GAA   | AUCGACCC   | GGGUCGAUU UCAAACCU  |
| 754         | GAGGUUUG  | CUGAUGA   | x   | GAA   | AAUCGACC   | GGUCGAUUU CAAACCUC  |
| <b>75</b> 5 | UGAGGUUU  | CUGAUGA   | X   | GAA   | AAAUCGAC   | GUCGAUUUC AAACCUCA  |
| 762         | GACACAUU  | CUGAUGA   | x   | GAA   | AGGUUUGA   | UCAAACCUC AAUGUGUC  |
| 770         | CGCAAAGA  | CUGAUGA   | x   | GAA   | ACACAUUG   | CAAUGUGUC UCUUUGCG  |
| 772         | AGCGCAAA  | CUGAUGA   | x   | GAA   | AGACACAU   | AUGUGUCUC UUUGCGCU  |
| 774         | CUAGCGCA  | CUGAUGA   | x   | GAA   | AGAGACAC   | GUGUCUCUU UGCGCUAG  |
| 775         | CCUAGCGC  | CUGAUGA   | x   | GAA   | AAGAGACA   | UGUCUCUUU GCGCUAGG  |
| 781         | UGGAUACC  | CUGAUGA   | x   | GAA   | AGCGCAAA   | UUUGCGCUA GGUAUCCA  |
| 785         | UUUCUGGA  | CUGAUGA   | x   | GAA   | ACCUAGCG   | CGCUAGGUA UCCAGAAA  |
| 787         | CUUUUCUG  | CUGAUGA   | X   | GAA   | AUACCUAG   | CUAGGUAUC CAGAAAAG  |
| 800         | CCGGAACA  | CUGAUGA   | X   | GAA   | AUCUCUUU   | AAAGAGAUU UGUUCCGG  |
| 801         | UCCGGAAC  | CUGAUGA   | X   | GAA   | AAUCUCUU   | AAGAGAUUU GUUCCGGA  |
| 804         | CCAUCCGG  | CUGAUGA   | X   | GAA   | ACAAAUCU   | AGAUUUGUU CCGGAUGG  |
| 805         | UCCAUCCG  | CUGAUGA   | X   | GAA   | AACAAAUC   | GAUUUGUUC CGGAUGGA  |
| 822         | UCCCAGGA  | CUGAUGA   | X   | GAA   | AUUCUGUU   | AACAGAAUU UCCUGGGA  |
| 823         | GUCCCAGG  | CUGAUGA   | X   | GAA   | AAUUCUGU   | ACAGAAUUU CCUGGGAC  |
| 824         | UGUCCCAG  | CUGAUGA   | X   | GAA   | AAAUUCUG   | CAGAAUUUC CUGGGACA  |
| 840         | GUAAAGCC  | CUGAUGA   | X   | GAA   | AUCUCGCU   | AGCGAGAUA GGCUUUAC  |
| 845         | GGAGAGUA  | CUGAUGA   | X   | GAA   | AGCCUAUC   | GAUAGGCUU UACUCUCC  |
|             | 669<br>674<br>678<br>696<br>701<br>705<br>735<br>749<br>753<br>754<br>755<br>762<br>770<br>772<br>774<br>775<br>781<br>785<br>787<br>800<br>801<br>804<br>805<br>822<br>823<br>824<br>840 | 666 GAGGCGAU 669 ACAGAGGC 674 CACUGACA 678 UGGUCACU 696 AUGUACAC 701 CGGUGAUG 705 UUCUCGGU 735 CGGCAGGG 749 UUGAAAUC 753 AGGUUUGA 754 GAGGUUUG 755 UGAGGUUU 770 CGCAAAGA 772 AGCGCAAA 772 AGCGCAAA 774 CUAGCGCA 775 CCUAGCGC 781 UGGAUACC 785 UUUCUGGA 787 CUUUUCUG 800 CCGGAACA 801 UCCGGAAC 801 UCCGGAAC 804 CCAUCCGG 805 UCCCAGGA 822 UCCCAGGA 823 GUCCCAGG 824 UGUCCCAG | 666 GAGGCGAU CUGAUGA 669 ACAGAGGC CUGAUGA 674 CACUGACA CUGAUGA 678 UGGUCACU CUGAUGA 696 AUGUACAC CUGAUGA 701 CGGUGAUG CUGAUGA 705 UUCUCGGU CUGAUGA 735 CGGCAGGG CUGAUGA 749 UUGAAAUC CUGAUGA 754 GAGGUUUG CUGAUGA 755 UGAGGUUU CUGAUGA 757 CGCAAAGA CUGAUGA 770 CGCAAAGA CUGAUGA 771 CUAGCGCA CUGAUGA 771 CUAGCGCA CUGAUGA 772 AGCGCAAA CUGAUGA 773 CCUAGCGC CUGAUGA 774 CUAGCGCA CUGAUGA 775 CCUAGCGC CUGAUGA 781 UGGAUACC CUGAUGA 787 CUUUUCUG CUGAUGA 787 CUUUUCUG CUGAUGA 800 CCGGAACA CUGAUGA 801 UCCGGAAC CUGAUGA 801 UCCGGAAC CUGAUGA 802 CCGAACA CUGAUGA 803 CCCAUCCG CUGAUGA 804 CCAUCCGG CUGAUGA 805 UCCAUCCG CUGAUGA 806 CCGAGGA CUGAUGA 807 CUGAUCCG CUGAUGA 808 CCCAUCCGG CUGAUGA 809 CCCAUCCGG CUGAUGA 800 CCCAUCCGG CUGAUGA 801 CCCAUCCGG CUGAUGA 802 UCCCAGGA CUGAUGA | 666 GAGGCGAU CUGAUGA X 669 ACAGAGGC CUGAUGA X 678 UGGUCACU CUGAUGA X 696 AUGUACAC CUGAUGA X 701 CGGUGAUG CUGAUGA X 705 UUCUCGGU CUGAUGA X 735 CGGCAGGG CUGAUGA X 749 UUGAAAUC CUGAUGA X 754 GAGGUUUG CUGAUGA X 755 UGAGGUUU CUGAUGA X 755 UGAGGUUU CUGAUGA X 757 CGCAAAGA CUGAUGA X 770 CGCAAAGA CUGAUGA X 771 CUAGCGCA CUGAUGA X 771 CUAGCGCA CUGAUGA X 772 AGCGCAAA CUGAUGA X 773 CCUAGCGC CUGAUGA X 774 CUAGCGCA CUGAUGA X 787 CUUUUCUG CUGAUGA X 787 CUUUUCUG CUGAUGA X 801 UCCGGAACA CUGAUGA X 801 CCGGAACA CUGAUGA X 801 CCGGAACA CUGAUGA X 801 CCCAUCCG CUGAUGA X 802 CCGGAACA CUGAUGA X 803 CCCAUCCG CUGAUGA X 804 CCAUCCGG CUGAUGA X 805 UCCCAGGA CUGAUGA X 806 CCGGAACA CUGAUGA X 807 CUGAUCCG CUGAUGA X 808 CCAUCCGG CUGAUGA X 809 CCGGAACA CUGAUGA X 809 CCGGAACA CUGAUGA X 800 CCGGAACA CUGAUGA X 801 UCCCAGGA CUGAUGA X 801 UCCCAGGA CUGAUGA X 802 UCCCAGGA CUGAUGA X 803 GUCCCAGG CUGAUGA X 804 CCAUCCGG CUGAUGA X 805 UCCCAGGA CUGAUGA X 806 CCGAGGA CUGAUGA X 807 CUGAUGA X 808 CCGAGGA CUGAUGA X 809 CCCAGGA CUGAUGA X 809 CCCAGGA CUGAUGA X 800 CCGAGGA CUGAUGA X 801 UCCCAGGA CUGAUGA X | 666 GAGGCGAU CUGAUGA X GAA 669 ACAGAGGC CUGAUGA X GAA 674 CACUGACA CUGAUGA X GAA 678 UGGUCACU CUGAUGA X GAA 696 AUGUACAC CUGAUGA X GAA 701 CGGUGAUG CUGAUGA X GAA 705 UUCUCGGU CUGAUGA X GAA 735 CGGCAGGG CUGAUGA X GAA 749 UUGAAAUC CUGAUGA X GAA 753 AGGUUUGA CUGAUGA X GAA 754 GAGGUUUG CUGAUGA X GAA 755 UGAGGUUU CUGAUGA X GAA 756 GACACAUU CUGAUGA X GAA 770 CGCAAAGA CUGAUGA X GAA 770 CGCAAAGA CUGAUGA X GAA 771 CUAGCGCA CUGAUGA X GAA 771 CUAGCGCA CUGAUGA X GAA 772 AGCGCAAA CUGAUGA X GAA 774 CUAGCGCA CUGAUGA X GAA 775 CCUAGCGC CUGAUGA X GAA 781 UGGAUACC CUGAUGA X GAA 787 CUUUUCUG CUGAUGA X GAA 787 CUUUUCUG CUGAUGA X GAA 787 CUUUUCUG CUGAUGA X GAA 800 CCGGAACA CUGAUGA X GAA 801 UCCGGAAC CUGAUGA X GAA 801 UCCGGAAC CUGAUGA X GAA 801 UCCGGAAC CUGAUGA X GAA 802 CCGCAAC CUGAUGA X GAA 803 CCGCAAC CUGAUGA X GAA 804 CCAUCCGG CUGAUGA X GAA 805 UCCAUCCG CUGAUGA X GAA 806 CCAUCCGG CUGAUGA X GAA 807 CUCCAUCCG CUGAUGA X GAA 808 CCAUCCGG CUGAUGA X GAA 809 CCCAUCCGG CUGAUGA X GAA 800 CCGGAACA CUGAUGA X GAA 801 UCCGGAAC CUGAUGA X GAA 801 UCCGGAAC CUGAUGA X GAA 802 UCCCAGGA CUGAUGA X GAA 803 GUCCCAGG CUGAUGA X GAA 804 CCAUCCGG CUGAUGA X GAA 805 UCCCAGGA CUGAUGA X GAA 806 GUAAAGCC CUGAUGA X GAA 807 GUCCCAGG CUGAUGA X GAA | ACAGAGGC CUGAUGA X GAA AUGAAUGG 674 CACUGACA CUGAUGA X GAA AGGCGAUG 678 UGGUCACU CUGAUGA X GAA ACAGAGGC 696 AUGUACAC CUGAUGA X GAA AUGCCAUG 701 CGGUGAUG CUGAUGA X GAA AUGUACAC 705 UUCUCGGU CUGAUGA X GAA AUGUACAC 735 CGGCAGGG CUGAUGA X GAA AUGUACAC 749 UUGAAAUC CUGAUGA X GAA AUCGACCC 753 AGGUUUGA CUGAUGA X GAA AUCGACCC 754 GAGGUUUG CUGAUGA X GAA AUCGACC 755 UGAGGUUU CUGAUGA X GAA AAUCGACC 762 GACACAUU CUGAUGA X GAA AAUCGAC 770 CGCAAAGA CUGAUGA X GAA ACACAUUG 771 CUAGCGCA CUGAUGA X GAA ACACAUUG 772 AGCGCAAA CUGAUGA X GAA AGACACAU 774 CUAGCGCC CUGAUGA X GAA AGAGACAC 775 CCUAGCGC CUGAUGA X GAA AGAGACAC 775 CCUAGCGC CUGAUGA X GAA AGAGACAC 776 CUUUUCUG CUGAUGA X GAA AGAGACAC 777 CUUUCUGGA CUGAUGA X GAA ACCUAGCG 787 CUUUUCUG CUGAUGA X GAA ACCUAGCG 787 CUUUUCUG CUGAUGA X GAA AUCCUCUU 800 CCGGAACA CUGAUGA X GAA AUCCUCUU 801 UCCGGAAC CUGAUGA X GAA AUCCUCUU 801 UCCGGAAC CUGAUGA X GAA AUCCUCUU 802 CUGAUGA X GAA ACAAAUCU 803 CCCGCAACA CUGAUGA X GAA ACAAAUCU 804 CCAUCCGG CUGAUGA X GAA ACAAAUCU 805 UCCCAGGA CUGAUGA X GAA AACAAAUCU 806 UCCAUCCG CUGAUGA X GAA ACAAAUCU 807 CCAUCCGG CUGAUGA X GAA ACAAAUCU 808 UCCCAGGA CUGAUGA X GAA ACAAAUCU 809 UCCCAGGA CUGAUGA X GAA ACAAAUCU 800 CCGGAACA CUGAUGA X GAA ACAAAUCU 801 UCCCAGGA CUGAUGA X GAA AACAAAUCU 802 UCCCAGGA CUGAUGA X GAA AACAAAUCU 803 GUCCCAGG CUGAUGA X GAA AACAAAUCU 804 CCAUCCGG CUGAUGA X GAA AACAAAUCU 805 UCCCAGGA CUGAUGA X GAA AACAAAUCU 806 UCCCAGGA CUGAUGA X GAA AACAAAUCU 807 GUAAAGCC CUGAUGA X GAA AACAAAUCU 808 GUCCCAGG CUGAUGA X GAA AACAAAUCU 809 GUAAAGCC CUGAUGA X GAA AACAAAUCU 800 GUAAAGCC CUGAUGA X GAA AAUCUCUGU |

|    | 846         | GGGAGAGU CUGAU   | GA . | X GA | A AAGCCUAU | AUAGGCUUU ACUCUCCC |
|----|-------------|------------------|------|------|------------|--------------------|
|    | 847         | GGGGAGAG CUGAU   | GA : | X GA | A AAAGCCUA | UAGGCUUUA CUCUCCCC |
|    | 850         | ACUGGGGA CUGAU   | GA : | X GA | A AGUAAAGC | GCUUUACUC UCCCCAGU |
|    | 852         | UAACUGGG CUGAU   | GA : | X GA | A AGAGUAAA | UUUACUCUC CCCAGUUA |
| 5  | 859         | GAUCAUGU CUGAU   | GA 2 | X GA | A ACUGGGGA | UCCCCAGUU ACAUGAUC |
|    | 860         | UGAUCAUG CUGAU   | GA 2 | K GA | A AACUGGGG | CCCCAGUUA CAUGAUCA |
|    | 867         | GCAUAGCU CUGAU   | GA 2 | GA/  | A AUCAUGUA | UACAUGAUC AGCUAUGC |
|    | 872         | UGCCGGCA CUGAU   | GA > | GA/  | A AGCUGAUC | GAUCAGCUA UGCCGGCA |
|    | <b>88</b> 5 | UCACAGAA CUGAU   | SA X | GA,  | ACCAUGCC   | GGCAUGGUC UUCUGUGA |
| 10 | 887         | CCUCACAG CUGAU   | K A  | GAA  | AGACCAUG   | CAUGGUCUU CUGUGAGG |
|    | 888         | GCCUCACA CUGAUG  | X AS | GAA  | AAGACCAU   | AUGGUCUUC UGUGAGGC |
|    | 903         | UCAUCAUU CUGAUG  | X A  | GAA  | AUCUUUGC   | GCAAAGAUC AAUGAUGA |
|    | 917         | UAGACUGA CUGAUG  | X A  | GAA  | AGGUUUCA   | UGAAACCUA UCAGUCUA |
|    | <b>9</b> 19 | GAUAGACU CUGAUG  | A X  | GAA  | AUAGGUUU   | AAACCUAUC AGUCUAUC |
| 15 | 923         | ACAUGAUA CUGAUG  | A X  | GAA  | ACUGAUAG   | CUAUCAGUC UAUCAUGU |
|    | 925         | GUACAUGA CUGAUG  | A X  | GAA  | AGACUGAU   | AUCAGUCUA UCAUGUAC |
|    | 927         | AUGUACAU CUGAUG  | A X  | GAA  | AUAGACUG   | CAGUCUAUC AUGUACAU |
|    | 932         | CAACUAUG CUGAUG  | АХ   | GAA  | ACAUGAUA   | UAUCAUGUA CAUAGUUG |
|    | 936         | ACCACAAC CUGAUG  | АХ   | GAA  | AUGUACAU   | AUGUACAUA GUUGUGGU |
| 20 | 939         | ACAACCAC CUGAUG  | A X  | GAA  | ACUAUGUA   | UACAUAGUU GUGGUUGU |
|    | 945         | UAUCCUAC CUGAUG  | A X  | GAA  | ACCACAAC   | GUUGUGGUU GUAGGAUA |
|    | 948         | CUAUAUCC CUGAUG  | A X  | GAA  | ACAACCAC   | GUGGUUGUA GGAUAUAG |
|    | 953         | AAAUCCUA CUGAUG  | A X  | GAA  | AUCCUACA   | UGUAGGAUA UAGGAUUU |
|    | 955         | AUAAAUCC CUGAUG  | A X  | GAA  | AUAUCCUA   | UAGGAUAUA GGAUUUAU |
| 25 | 960         | ACAUCAUA CUGAUGA | A X  | GAA  | AUCCUAUA   | UAUAGGAUU UAUGAUGU |
|    | 961         | CACAUCAU CUGAUGA | A X  | GAA  | AAUCCUAU   | AUAGGAUUU AUGAUGUG |
|    | 962         | UCACAUCA CUGAUGA | X A  | GAA  | AAAUCCUA   | UAGGAUUUA UGAUGUGA |
|    | 972         | GGGCUCAG CUGAUG  | X A  | GAA  | AUCACAUC   | GAUGUGAUU CUGAGCCC |
|    | 973         | GGGGCUCA CUGAUGI | X A  | GAA  | AAUCACAU   | AUGUGAUUC UGAGCCCC |
| 30 | 993         | GAUAGCUC CUGAUGA | X A  | GAA  | AUUUCAUG   | CAUGAAAUU GAGCUAUC |
|    |             |                  |      |      |            |                    |

|    | 999  | CCGGCAGA | CUGAUGA | Х | GAA | AGCUCAAU | AUUGAGCUA UCUGCCGG |
|----|------|----------|---------|---|-----|----------|--------------------|
|    | 1001 | CUCCGGCA | CUGAUGA | X | GAA | AUAGCUCA | UGAGCUAUC UGCCGGAG |
|    | 1017 | UUUAAGAC | CUGAUGA | X | GAA | AGUUUUUC | GAAAAACUU GUCUUAAA |
|    | 1020 | CAAUUUAA | CUGAUGA | X | GAA | ACAAGUUU | AAACUUGUC UUAAAUUG |
| 5  | 1022 | UACAAUUU | CUGAUGA | X | GAA | AGACAAGU | ACUUGUCUU AAAUUGUA |
|    | 1023 | GUACAAUU | CUGAUGA | X | GAA | AAGACAAG | CUUGUCUUA AAUUGUAC |
|    | 1027 | CGCUGUAC | CUGAUGA | x | GAA | AUUUAAGA | UCUUAAAUU GUACAGCG |
|    | 1030 | UCUCGCUG | CUGAUGA | X | GAA | ACAAUUUA | UAAAUUGUA CAGCGAGA |
|    | 1047 | CCCACAUU | CUGAUGA | x | GAA | AGCUCUGU | ACAGAGCUC AAUGUGGG |
| 10 | 1059 | GUGAAAUC | CUGAUGA | X | GAA | AGCCCCAC | GUGGGGCUU GAUUUCAC |
|    | 1063 | CCAGGUGA | CUGAUGA | X | GAA | AUCAAGCC | GGCUUGAUU UCACCUGG |
|    | 1064 | GCCAGGUG | CUGAUGA | x | GAA | AAUCAAGC | GCUUGAUUU CACCUGGC |
|    | 1065 | UGCCAGGU | CUGAUGA | X | GAA | AAAUCAAG | CUUGAUUUC ACCUGGCA |
|    | 1076 | AAGGUGGA | CUGAUGA | X | GAA | AGUGCCAG | CUGGCACUC UCCACCUU |
| 15 | 1078 | UGAAGGUG | CUGAUGA | X | GAA | AGAGUGCC | GGCACUCUC CACCUUCA |
|    | 1084 | AGACUUUG | CUGAUGA | X | GAA | AGGUGGAG | CUCCACCUU CAAAGUCU |
|    | 1085 | GAGACUUU | CUGAUGA | x | GAA | AAGGUGGA | UCCACCUUC AAAGUCUC |
|    | 1091 | UAUGAUGA | CUGAUGA | x | GAA | ACUUUGAA | UUCAAAGUC UCAUCAUA |
|    | 1093 | CUUAUGAU | CUGAUGA | X | GAA | AGACUUUG | CAAAGUCUC AUCAUAAG |
| 20 | 1096 | CUUCUUAU | CUGAUGA | X | GAA | AUGAGACU | AGUCUCAUC AUAAGAAG |
|    | 1099 | AAUCUUCU | CUGAUGA | X | GAA | AUGAUGAG | CUCAUCAUA AGAAGAUU |
|    | 1107 | CGGUUUAC | CUGAUGA | x | GAA | AUCUUCUU | AAGAAGAUU GUAAACCG |
|    | 1110 | UCCCGGUU | CUGAUGA | X | GAA | ACAAUCUU | AAGAUUGUA AACCGGGA |
|    | 1130 | UCCCAGGA | CUGAUGA | X | GAA | AGGGUUUC | GAAACCCUU UCCUGGGA |
| 25 | 1131 | GUCCCAGG | CUGAUGA | X | GAA | AAGGGUUU | AAACCCUUU CCUGGGAC |
|    | 1132 | AGUCCCAG | CUGAUGA | X | GAA | AAAGGGUU | AACCCUUUC CUGGGACU |
|    | 1154 | UGCUCAAA | CUGAUGA | x | GAA | ACAUCUUC | GAAGAUGUU UUUGAGCA |
|    | 1155 | GUGCUCAA | CUGAUGA | X | GAA | AACAUCUU | AAGAUGUUU UUGAGCAC |
| •  | 1156 | GGUGCUCA | CUGAUGA | X | GAA | AAACAUCU | AGAUGUUUU UGAGCACC |
| 30 | 1157 | AGGUGCUC | CUGAUGA | x | GAA | AAAACAUC | GAUGUUUUU GAGCACCU |

|            | 1100 | CUAUUGU     | CUGAUG    | A. 2       | ( GA | A AGGUGCUC | GAGCACCUU GACAAUA  |
|------------|------|-------------|-----------|------------|------|------------|--------------------|
|            | 1173 | ACACUUU     | CUGAUG    | A 2        | GA.  | A AUUGUCAA | UUGACAAUA GAAAGUGI |
|            | 1205 | CACAGGU     | CUGAUG    | <b>A</b> > | GA/  | A AUUCCCCU | AGGGGAAUA CACCUGUG |
|            | 1215 | CUGGACG     | CUGAUG    | <b>X</b>   | GAZ  | ACACAGGU   | ACCUGUGUA GCGUCCAG |
| 5          | 1220 | GUCCACU     | CUGAUGA   | X          | GAZ  | ACGCUACA   | UGUAGCGUC CAGUGGAC |
|            | 1236 | ייייכייכייו | J CUGAUGA | X          | GAA  | AUCAUCCG   | CGGAUGAUC AAGAGAAA |
|            | 1246 | AAAUGUUC    | CUGAUGA   | X X        | GAA  | AUUUCUCU   | AGAGAAAUA GAACAUUU |
|            | 1253 | CUCGGACA    | CUGAUGA   | X          | GAA  | AUGUUCUA   | UAGAACAUU UGUCCGAG |
|            | 1254 | ACUCGGAC    | CUGAUGA   | X          | GAA  | AAUGUUCU   | AGAACAUUU GUCCGAGU |
| 10         | 1257 | UGAACUCG    | CUGAUGA   | . x        | GAA  | ACAAAUGU   | ACAUUUGUC CGAGUUCA |
|            | 1263 | UUUGUGUG    | CUGAUGA   | X          | GAA  | ACUCGGAC   | GUCCGAGUU CACACAAA |
|            | 1264 | CUUUGUGU    | CUGAUGA   | x          | GAA  | AACUCGGA   | UCCGAGUUC ACACAAAG |
|            | 1276 | AGCAAUAA    | CUGAUGA   | X          | GAA  | AGGCUUUG   | CAAAGCCUU UUAUUGCU |
|            | 1277 | AAGCAAUA    | CUGAUGA   | x          | GAA  | AAGGCUUU   | AAAGCCUUU UAUUGCUU |
| 15         | 1278 | AAAGCAAU    | CUGAUGA   | X          | GAA  | AAAGGCUU   | AMCCCUUUU AUUGCUUU |
|            | 1279 | GAAAGCAA    | CUGAUGA   | X          | GAA  | AAAAGGCU   | AGCCUUUUA UUGCUUUC |
|            | 1281 | CCGAAAGC    | CUGAUGA   | x          | GAA  | AUAAAAGG   | CCUUUUAUU GCUUUCGG |
|            | 1285 | ACUACCGA    | CUGAUGA   | x          | GAA  | AGCAAUAA   | UUAUUGCUU UCGGUAGU |
|            | 1286 | CACUACCG    | CUGAUGA   | X          | GAA  | AAGCAAUA   | UAUUGCUUU CGGUAGUG |
| 20         | 1287 | CCACUACC    | CUGAUGA   | X          | GAA  | AAAGCAAU   | AUUGCUUUC GGUAGUGG |
|            | 1291 | CAUCCCAC    | CUGAUGA   | X          | GAA  | ACCGAAAG   | CUUUCGGUA GUGGGAUG |
|            | 1304 | CCACCAAA    | CUGAUGA   | X          | GAA  | AUUUCAUC   | GAUGAAAUC UUUGGUGG |
|            | 1306 | UUCCACCA    | CUGAUGA   | x          | GAA  | AGAUUUCA   | UGAAAUCUU UGGUGGAA |
|            | 1307 | CUUCCACC    | CUGAUGA   | X          | GAA  | AAGAUUUC   | GAAAUCUUU GGUGGAAG |
| <b>2</b> 5 | 1330 | UCGGACUU    | CUGAUGA   | X          | GAA  | ACUGCCCA   | UGGGCAGUC AAGUCCGA |
|            | 1335 | GGGAUUCG    | CUGAUGA   | x          | GAA  | ACUUGACU   | AGUCAAGUC CGAAUCCC |
|            |      |             |           |            |      |            | GUCCGAAUC CCUGUGAA |
|            |      |             |           |            |      |            | UGUGAAGUA UCUCAGUU |
|            |      |             |           |            |      |            | UGAAGUAUC UCAGUUAC |
| 30         | 1356 | GGGUAACU    | CUGAUGA   | X          | GAA  | AGAUACUU   | AAGUAUCUC AGUUACCC |
|            |      |             |           |            |      |            |                    |

|    | 1360 . | AGCUGGGU | CUGAUGA | X          | GAA | ACUGAGAU | AUCUCAGUU | ACCCAGCU |
|----|--------|----------|---------|------------|-----|----------|-----------|----------|
|    | 1361   | GAGCUGGG | CUGAUGA | x          | GAA | AACUGAGA | UCUCAGUUA | CCCAGCUC |
|    | 1369   | GAUAUCAG | CUGAUGA | X          | GAA | AGCUGGGU | ACCCAGCUC | CUGAUAUC |
|    | 1375   | CCAUUUGA | CUGAUGA | . <b>X</b> | GAA | AUCAGGAG | CUCCUGAUA | UCAAAUGG |
| 5  | 1377   | UACCAUUU | CUGAUGA | X          | GAA | AUAUCAGG | CCUGAUAUC | AAAUGGUA |
|    | 1385   | CAUUUCUG | CUGAUGA | x          | GAA | ACCAUUUG | CAAAUGGUA | CAGAAAUG |
|    | 1404   | UUGGACUC | CUGAUGA | x          | GAA | AUGGGCCU | AGGCCCAUU | GAGUCCAA |
|    | 1409 ( | UGUAGUUG | CUGAUGA | X          | GAA | ACUCAAUG | CAUUGAGUC | CAACUACA |
|    | 1415 ( | UCAUUGUG | CUGAUGA | X          | GAA | AGUUGGAC | GUCCAACUA | CACAAUGA |
| 10 | 1425 ( | UCGCCAAC | CUGAUGA | X          | GAA | AUCAUUGU | ACAAUGAUU | GUUGGCGA |
|    | 1428 ( | UCAUCGCC | CUGAUGA | X          | GAA | ACAAUCAU | AUGAUUGUU | GGCGAUGA |
|    | 1440 # | AUGAUGGU | CUGAUGA | x          | GAA | AGUUCAUC | GAUGAACUC | ACCAUCAU |
|    | 1446 A | ACUUCCAU | CUGAUGA | X          | GAA | AUGGUGAG | CUCACCAUC | AUGGAAGU |
|    | 1478 ( | JGACCGUG | CUGAUGA | X          | GAA | AGUUUCCU | AGGAAACUA | CACGGUCA |
| 15 | 1485 0 | SUGAGGAU | CUGAUGA | X          | GAA | ACCGUGUA | UACACGGUC | AUCCUCAC |
|    | 1488 U | JUGGUGAG | CUGAUGA | x          | GAA | AUGACCGU | ACGGUCAUC | CUCACCAA |
|    | 1491 G | GGUUGGU  | CUGAUGA | x          | GAA | AGGAUGAC | GUCAUCCUC | ACCAACCC |
|    | 1503 U | JCCAUUGA | CUGAUGA | X          | GAA | AUGGGGUU | AACCCCAUU | UCAAUGGA |
|    | 1504 C | CUCCAUUG | CUGAUGA | X          | GAA | AAUGGGGU | ACCCCAUUU | CAAUGGAG |
| 20 | 1505 U | CUCCAUU  | CUGAUGA | X          | GAA | AAAUGGGG | CCCCAUUUC | AAUGGAGA |
|    | 1530 A | CCAGAGA  | CUGAUGA | X          | GAA | ACCAUGUG | CACAUGGUC | UCUCUGGU |
|    | 1532 C | AACCAGA  | CUGAUGA | X          | GAA | AGACCAUG | CAUGGUCUC | UCUGGUUG |
| •  | 1534 C | ACAACCA  | CUGAUGA | X          | GAA | AGAGACCA | UGGUCUCUC | UGGUUGUG |
|    | 1539 A | CAUUCAC  | CUGAUGA | x          | GAA | ACCAGAGA | UCUCUGGUU | GUGAAUGU |
| 25 | 1548 U | GGGGUGG  | CUGAUGA | X          | GAA | ACAUUCAC | GUGAAUGUC | CCACCCCA |
|    | 1560 U | UCUCACC  | CUGAUGA | X          | GAA | AUCUGGGG | CCCCAGAUC | GGUGAGAA |
|    | 1574 G | CGAGAUC  | CUGAUGA | X          | GAA | AGGCUUUC | GAAAGCCUU | GAUCUCGC |
|    | 1578 A | UAGGCGA  | CUGAUGA | x          | GAA | AUCAAGGC | GCCUUGAUC | UCGCCUAU |
|    | 1580 C | CAUAGGC  | CUGAUGA | X          | GAA | AGAUCAAG | CUUGAUCUC | GCCUAUGG |
| 30 | 1585 G | GAAUCCA  | CUGAUGA | X          | GAA | AGGCGAGA | UCUCGCCUA | UGGAUUCC |

|    | 159  | 1 CUGGUAG | G CUGAUG | Α          | X GA | A AUCCAUAC | CUAUGGAUU CCUACCAG |
|----|------|-----------|----------|------------|------|------------|--------------------|
|    | 159  | 2 ACUGGUA | G CUGAUG | A          | X GA | A AAUCCAUA | UAUGGAUUC CUACCAGU |
|    | 159  | 5 CAUACUG | G CUGAUG | <b>A</b> : | X GA | A AGGAAUCC |                    |
|    | 160  | 1 UGGUCCC | A CUGAUG | <b>A</b> : | X GA | A ACUGGUAG |                    |
| 5  | 1619 | UGCAUGU   | C CUGAUG | A 2        | K GA | A AUGUCUGC |                    |
|    | 1632 | 2 UUGGCGU | A CUGAUG | A J        | K GA | A ACUGUGCA |                    |
|    | 1634 | GGUUGGC   | G CUGAUG | A 2        | ( GA | A AGACUGUG |                    |
|    | 1645 | GUGCAGG   | G CUGAUG | <b>A</b> 2 | GA)  | A AGGGUUGG |                    |
|    | 1659 | UACCACUO  | CUGAUG   | X A        | GA   | A AUGUGGUG |                    |
| 10 | 1667 | GCUGCCAG  | CUGAUGA  | X A        | GAZ  | ACCACUGG   | CCAGUGGUA CUGGCAGC |
|    | 1677 | GCUUCUUC  | CUGAUGA  | X          | GAZ  | AGCUGCCA   | UGGCAGCUA GAAGAAGC |
|    | 1691 | GUCUGUAG  | CUGAUGA  | X          | GAA  | AGCAGGCU   | AGCCUGCUC CUACAGAC |
|    | 1694 | CGGGUCUG  | CUGAUGA  | X          | GAA  | AGGAGCAG   | CUGCUCCUA CAGACCCG |
|    | 1718 | UACAAGCA  | CUGAUGA  | X          | GAA  | ACGGGCUU   | AAGCCCGUA UGCUUGUA |
| 15 | 1723 | UUCUUUAC  | CUGAUGA  | x          | GAA  | AGCAUACG   | CGUAUGCUU GUAAAGAA |
|    | 1726 | CCAUUCUU  | CUGAUGA  | X          | GAA  | ACAAGCAU   | AUGCUUGUA AAGAAUGG |
|    |      |           |          |            |      | AUCCUCCA   | UGGAGGAUU UCCAGGGG |
|    | 1751 | CCCCCUGG  | CUGAUGA  | X          | GAA  | AAUCCUCC   | GGAGGAUUU CCAGGGGG |
|    |      | CCCCCCUG  |          |            |      |            | GAGGAUUUC CAGGGGGG |
| 20 | 1770 | GUGACUUC  | CUGAUGA  | X          | GAA  | AUCUUGUU   | AACAAGAUC GAAGUCAC |
|    |      | UUUUUGGU  |          |            |      |            | AUCGAAGUC ACCAAAAA |
|    |      | UCAGGGCA  |          |            |      |            | AAACCAAUA UGCCCUGA |
|    |      | חחהכחחה   |          |            |      |            | GCCCUGAUU GAAGGAAA |
|    |      |           |          |            |      | ACAGUUUU   | AAAACUGUA AGUACGCU |
| 25 |      | GACCAGCG  |          |            |      |            | CUGUAAGUA CGCUGGUC |
|    |      |           |          |            |      |            | ACGCUGGUC AUCCAAGC |
|    |      | GCAGCUUG  |          |            |      |            | CUGGUCAUC CAAGCUGC |
|    |      |           |          |            |      |            | CAACGUGUC AGCGUUGU |
|    |      |           |          |            |      |            | GUCAGCGUU GUACAAAU |
| 30 | 1862 | CACAUUUG  | CUGAUGA  | X          | GAA  | ACAACGCU   | AGCGUUGUA CAAAUGUG |

|    | 1878 GCUUUGUU CUGAUGA X GAA AUGGCU   | JC GAAGCCAUC AACAAAGC |
|----|--------------------------------------|-----------------------|
|    | 1905 AAGGAGAU CUGAUGA X GAA ACCCUCU  | JC GAGAGGGUC AUCUCCUU |
|    | 1908 UGGAAGGA CUGAUGA X GAA AUGACCO  |                       |
|    | 1910 CAUGGAAG CUGAUGA X GAA AGAUGAC  |                       |
| 5  | 1913 UCACAUGG CUGAUGA X GAA AGGAGAU  |                       |
|    | 1914 AUCACAUG CUGAUGA X GAA AAGGAGA  |                       |
|    | 1923 GGACCCCU CUGAUGA X GAA AUCACAU  | G CAUGUGAUC AGGGGUCC  |
|    | 1930 AAUUUCAG CUGAUGA X GAA ACCCCUG  |                       |
|    | 1938 UGCACAGU CUGAUGA X GAA AUUUCAG  |                       |
| 10 | 1939 UUGCACAG CUGAUGA X GAA AAUUUCA  | G CUGAAAUUA CUGUGCAA  |
|    | 1982 ACAACAGG CUGAUGA X GAA ACACACU  | C GAGUGUGUC CCUGUUGU  |
|    | 1988 CAGUGCAC CUGAUGA X GAA ACAGGGA  | C GUCCCUGUU GUGCACUG  |
|    | 2008 CUCAAACG CUGAUGA X GAA AUUUCUG  | U ACAGAAAUA CGUUUGAG  |
|    | 2012 GGUUCUCA CUGAUGA X GAA ACGUAUU  | U AAAUACGUU UGAGAACC  |
| 15 | 2013 AGGUUCUC CUGAUGA X GAA AACGUAU  | J AAUACGUUU GAGAACCU  |
|    | 2022 UACCACGU CUGAUGA X GAA AGGUUCU  | GAGAACCUC ACGUGGUA    |
|    | 2030 CAAGCUUG CUGAUGA X GAA ACCACGU  | G CACGUGGUA CAAGCUUG  |
|    | 2037 UGUGAGCC CUGAUGA X GAA AGCUUGUA | UACAAGCUU GGCUCACA    |
|    | 2042 UUGCCUGU CUGAUGA X GAA AGCCAAGG | GCUUGGCUC ACAGGCAA    |
| 20 | 2054 UGUGGACC CUGAUGA X GAA AUGUUGCO | GGCAACAUC GGUCCACA    |
|    | 2058 CCCAUGUG CUGAUGA X GAA ACCGAUGU | ACAUCGGUC CACAUGGG    |
|    | 2072 GUGUGAGU CUGAUGA X GAA AUUCGCCC | GGGCGAAUC ACUCACAC    |
|    | 2076 ACUGGUGU CUGAUGA X GAA AGUGAUUC | GAAUCACUC ACACCAGU    |
|    | 2085 UUCUUGCA CUGAUGA X GAA ACUGGUGU | ACACCAGUU UGCAAGAA    |
| 25 | 2086 GUUCUUGC CUGAUGA X GAA AACUGGUG | CACCAGUUU GCAAGAAC    |
|    | 2096 GAGCAUCC CUGAUGA X GAA AGUUCUUG | CAAGAACUU GGAUGCUC    |
|    | 2104 UUUCCAAA CUGAUGA X GAA AGCAUCCA | UGGAUGCUC UUUGGAAA    |
|    | 2106 AGUUUCCA CUGAUGA X GAA AGAGCAUC | GAUGCUCUU UGGAAACU    |
|    | 2107 CAGUUUCC CUGAUGA X GAA AAGAGCAU | AUGCUCUUU GGAAACUG    |
| 30 | 2129 UGUUAGAA CUGAUGA X GAA ACAUGGUG | CACCAUGUU UUCUAACA    |

|    | 2130 CUGUUAGA CUGAUGA X GAA AACAUGGU | ACCAUGUUU UCUAACAG |
|----|--------------------------------------|--------------------|
|    | 2131 GCUGUUAG CUGAUGA X GAA AAACAUGG | CCAUGUUUU CUAACAGC |
|    | 2132 UGCUGUUA CUGAUGA X GAA AAAACAUG | CAUGUUUUC UAACAGCA |
|    | 2134 UGUGCUGU CUGAUGA X GAA AGAAAACA | UGUUUUCUA ACAGCACA |
| 5  | 2151 ACAAUCAA CUGAUGA X GAA AUGUCAUU | AAUGACAUC UUGAUUGU |
|    | 2153 CCACAAUC CUGAUGA X GAA AGAUGUCA | UGACAUCUU GAUUGUGG |
|    | 2157 AAUGCCAC CUGAUGA X GAA AUCAAGAU | AUCUUGAUU GUGGCAUU |
|    | 2165 CAUUCUGA CUGAUGA X GAA AUGCCACA | UGUGGCAUU UCAGAAUG |
|    | 2166 GCAUUCUG CUGAUGA X GAA AAUGCCAC | GUGGCAUUU CAGAAUGC |
| 10 | 2167 GGCAUUCU CUGAUGA X GAA AAAUGCCA | UGGCAUUUC AGAAUGCC |
|    | 2177 CCUGCAGA CUGAUGA X GAA AGGCAUUC | GAAUGCCUC UCUGCAGG |
|    | 2179 GUCCUGCA CUGAUGA X GAA AGAGGCAU | AUGCCUCUC UGCAGGAC |
|    | 2198 AGCAAACA CUGAUGA X GAA AGUCGCCU | AGGCGACUA UGUUUGCU |
|    | 2202 GCAGAGCA CUGAUGA X GAA ACAUAGUC | GACUAUGUU UGCUCUGC |
| 15 | 2203 AGCAGAGC CUGAUGA X GAA AACAUAGU | ACUAUGUUU GCUCUGCU |
|    | 2207 CUUGAGCA CUGAUGA X GAA AGCAAACA | UGUUUGCUC UGCUCAAG |
|    | 2212 CUUAUCUU CUGAUGA X GAA AGCAGAGC | GCUCUGCUC AAGAUAAG |
|    | 2218 GGUCUUCU CUGAUGA X GAA AUCUUGAG | CUCAAGAUA AGAAGACC |
|    | 2239 GACCAGGC CUGAUGA X GAA AUGUCUUU | AAAGACAUU GCCUGGUC |
| 20 | 2247 AGCUGUUU CUGAUGA X GAA ACCAGGCA | UGCCUGGUC AAACAGCU |
|    | 2256 AGGAUGAU CUGAUGA X GAA AGCUGUUU | AAACAGCUC AUCAUCCU |
|    | 2259 UCUAGGAU CUGAUGA X GAA AUGAGCUG | CAGCUCAUC AUCCUAGA |
|    | 2262 CGCUCUAG CUGAUGA X GAA AUGAUGAG | CUCAUCAUC CUAGAGCG |
|    | 2265 AUGCGCUC CUGAUGA X GAA AGGAUGAU | AUCAUCCUA GAGCGCAU |
| 25 | 2286 UUUCCGGU CUGAUGA X GAA AUCAUGGG | CCCAUGAUC ACCGGAAA |
|    | 2296 AUUCUCCA CUGAUGA X GAA AUUUCCGG | CCGGAAAUC UGGAGAAU |
|    | 2305 UGUUGUCU CUGAUGA X GAA AUUCUCCA | UGGAGAAUC AGACAACA |
|    | 2319 GUCUCGCC CUGAUGA X GAA AUGGUUGU | ACAACCAUU GGCGAGAC |
|    |                                      | GAGACCAUU GAAGUGAC |
| 30 | 2341 UGCUGGGC CUGAUGA X GAA AGUCACUU | AAGUGACUU GCCCAGCA |

|    | 2351 GAUUUCC  | A CUGAUGA | X          | GAA | AUGCUGGG | CCCAGCAUC UGGAAAUC |
|----|---------------|-----------|------------|-----|----------|--------------------|
|    | 2359 UGGGGUA  | G CUGAUGA | X          | GAA | AUUUCCAG | CUGGAAAUC CUACCCCA |
|    | 2362 GUGUGGG  | G CUGAUGA | . <b>x</b> | GAA | AGGAUUUC | GAAAUCCUA CCCCACAC |
|    | 2373 AACCAUG  | U CUGAUGA | . <b>x</b> | GAA | AUGUGUGG | CCACACAUU ACAUGGUU |
| 5  | 2374 GAACCAU  | g Cugauga | X          | GAA | AAUGUGUG | CACACAUUA CAUGGUUC |
|    | 2381 UGUCUUU  | g Cugauga | X          | GAA | ACCAUGUA | UACAUGGUU CAAAGACA |
|    | 2382 UUGUCUU  | U CUGAUGA | X          | GAA | AACCAUGU | ACAUGGUUC AAAGACAA |
|    | 2403 GAAUCUU  | C CUGAUGA | X          | GAA | ACCAGGGU | ACCCUGGUA GAAGAUUC |
|    | 2410 AAUGCCU  | G CUGAUGA | x          | GAA | AUCUUCUA | UAGAAGAUU CAGGCAUU |
| 10 | 2411 CAAUGCCU | J CUGAUGA | x          | GAA | AAUCUUCU | AGAAGAUUC AGGCAUUG |
|    | 2418 CUCAGUA  | CUGAUGA   | x          | GAA | AUGCCUGA | UCAGGCAUU GUACUGAG |
|    | 2421 UCUCUCAC | CUGAUGA   | x          | GAA | ACAAUGCC | GGCAUUGUA CUGAGAGA |
|    | 2449 CCUGCGG  | CUGAUGA   | x          | GAA | AGUCAGGU | ACCUGACUA UCCGCAGG |
|    | 2451 ACCCUGCO | CUGAUGA   | x          | GAA | AUAGUCAG | CUGACUAUC CGCAGGGU |
| 15 | 2481 CAGGUGUA | CUGAUGA   | x          | GAA | AGGCCUCC | GGAGGCCUC UACACCUG |
|    | 2483 GGCAGGUG | CUGAUGA   | x          | GAA | AGAGGCCU | AGGCCUCUA CACCUGCC |
|    | 2505 CAGCCAAG | CUGAUGA   | x          | GAA | ACAUUGCA | UGCAAUGUC CUUGGCUG |
|    | 2508 GCACAGCO | CUGAUGA   | x          | GAA | AGGACAUU | AAUGUCCUU GGCUGUGC |
|    | 2532 AUUAUGAA | CUGAUGA   | x          | GAA | AGCGUCUC | GAGACGCUC UUCAUAAU |
| 20 | 2534 CUAUUAUG | CUGAUGA   | X          | GAA | AGAGCGUC | GACGCUCUU CAUAAUAG |
|    | 2535 UCUAUUAU | CUGAUGA   | x          | GAA | AAGAGCGU | ACGCUCUUC AUAAUAGA |
|    | 2538 CCUUCUAU | CUGAUGA   | x          | GAA | AUGAAGAG | CUCUUCAUA AUAGAAGG |
|    | 2541 GCACCUUC | CUGAUGA   | X          | GAA | AUUAUGAA | UUCAUAAUA GAAGGUGC |
|    | 2567 UGACUUCC | CUGAUGA   | X          | GAA | AGUUGGUC | GACCAACUU GGAAGUCA |
| 25 | 2574 AGGAUAAU | CUGAUGA   | X          | GAA | ACUUCCAA | UUGGAAGUC AUUAUCCU |
|    | 2577 ACGAGGAU | CUGAUGA   | x          | GAA | AUGACUUC | GAAGUCAUU AUCCUCGU |
|    | 2578 GACGAGGA | CUGAUGA   | x          | GAA | AAUGACUU | AAGUCAUUA UCCUCGUC |
|    | 2580 CCGACGAG | CUGAUGA   | X          | GAA | AUAAUGAC | GUCAUUAUC CUCGUCGG |
|    | 2583 GUGCCGAC | CUGAUGA   | X          | GAA | AGGAUAAU | AUUAUCCUC GUCGGCAC |
| 30 | 2586 GCAGUGCC | CUGAUGA   | X ·        | GAA | ACGAGGAU | AUCCUCGUC GGCACUGC |

|    | 2601 | AACAUGGC | CUGAUGA | . x | GAA | AUCACUGC | GCAGUGAUU GCCAUGUU |
|----|------|----------|---------|-----|-----|----------|--------------------|
|    | 2609 | GCCAGAAG | CUGAUGA | X   | GAA | ACAUGGCA | UGCCAUGUU CUUCUGGC |
|    | 2610 | AGCCAGAA | CUGAUGA | X   | GAA | AACAUGGC | GCCAUGUUC UUCUGGCU |
|    | 2612 | GGAGCCAG | CUGAUGA | X   | GAA | AGAACAUG | CAUGUUCUU CUGGCUCC |
| 5  | 2613 | AGGAGCCA | CUGAUGA | X   | GAA | AAGAACAU | AUGUUCUUC UGGCUCCU |
|    | 2619 | ACAAGAAG | CUGAUGA | x   | GAA | AGCCAGAA | UUCUGGCUC CUUCUUGU |
|    | 2622 | AUGACAAG | CUGAUGA | x   | GAA | AGGAGCCA | UGGCUCCUU CUUGUCAU |
|    | 2623 | AAUGACAA | CUGAUGA | x   | GAA | AAGGAGCC | GGCUCCUUC UUGUCAUU |
|    | 2625 | ACAAUGAC | CUGAUGA | X   | GAA | AGAAGGAG | CUCCUUCUU GUCAUUGU |
| 10 | 2628 | AGGACAAU | CUGAUGA | x   | GAA | ACAAGAAG | CUUCUUGUC AUUGUCCU |
|    | 2631 | CGUAGGAC | CUGAUGA | x   | GAA | AUGACAAG | CUUGUCAUU GUCCUACG |
|    | 2634 | GUCCGUAG | CUGAUGA | x   | GAA | ACAAUGAC | GUCAUUGUC CUACGGAC |
|    | 2637 | ACGGUCCG | CUGAUGA | X   | GAA | AGGACAAU | AUUGUCCUA CGGACCGU |
|    | 2646 | GCCCGCUU | CUGAUGA | x   | GAA | ACGGUCCG | CGGACCGUU AAGCGGGC |
| 15 | 2647 | GGCCCGCU | CUGAUGA | Y.  | GAA | AACGGUCC | GGACCGUUA AGCGGGCC |
|    | 2681 | UAGACAAG | CUGAUGA | X   | GAA | AGCCUGUC | GACAGGCUA CUUGUCUA |
|    | 2684 | CAAUAGAC | CUGAUGA | x   | GAA | AGUAGCCU | AGGCUACUU GUCUAUUG |
|    | 2687 | UGACAAUA | CUGAUGA | x   | GAA | ACAAGUAG | CUACUUGUC UAUUGUCA |
|    | 2689 | CAUGACAA | CUGAUGA | x   | GAA | AGACAAGU | ACUUGUCUA UUGUCAUG |
| 20 | 2691 | UCCAUGAC | CUGAUGA | x   | GAA | AUAGACAA | UUGUCUAUU GUCAUGGA |
|    | 2694 | GGAUCCAU | CUGAUGA | X   | GAA | ACAAUAGA | UCUAUUGUC AUGGAUCC |
|    | 2701 | UUCAUCUG | CUGAUGA | x   | GAA | AUCCAUGA | UCAUGGAUC CAGAUGAA |
|    | 2711 | CCAAGGGC | CUGAUGA | X   | GAA | AUUCAUCU | AGAUGAAUU GCCCUUGG |
|    | 2717 | GCUCAUCC | CUGAUGA | Х   | GAA | AGGGCAAU | AUUGCCCUU GGAUGAGC |
| 25 | 2738 | CAUAAGGC | CUGAUGA | x   | GAA | AGCGUUCA | UGAACGCUU GCCUUAUG |
|    | 2743 | GGCAUCAU | CUGAUGA | x   | GAA | AGGCAAGC | GCUUGCCUU AUGAUGCC |
|    | 2744 | UGGCAUCA | CUGAUGA | x   | GAA | AAGGCAAG | CUUGCCUUA UGAUGCCA |
|    | 2765 | CCCUGGGG | CUGAUGA | X   | GAA | AUUCCCAC | GUGGGAAUU CCCCAGGG |
|    | 2766 | UCCCUGGG | CUGAUGA | x   | GAA | AAUUCCCA | UGGGAAUUC CCCAGGGA |
| 30 | 2787 | GGUUUUCC | CUGAUGA | X   | GAA | AGUUUCAG | CUGAAACUA GGAAAACC |

|    | 2797 | GCGGCCA  | A CUGAUGA | X          | GAA | AGGUUUUC | GAAAACCUC UUGGCCGC |
|----|------|----------|-----------|------------|-----|----------|--------------------|
|    | 2799 | CCGCGGCC | CUGAUGA   | X          | GAA | AGAGGUUU | AAACCUCUU GGCCGCGG |
|    | 2813 | CUUGGCCG | CUGAUGA   | X          | GAA | AGGCACCG | CGGUGCCUU CGGCCAAG |
|    | 2814 | ACUUGGCC | CUGAUGA   | x          | GAA | AAGGCACC | GGUGCCUUC GGCCAAGU |
| 5  | 2826 | ucugccuc | CUGAUGA   | . <b>x</b> | GAA | AUCACUUG | CAAGUGAUU GAGGCAGA |
|    | 2839 | AAUUCCAA | CUGAUGA   | X          | GAA | AGCGUCUG | CAGACGCUU UUGGAAUU |
|    | 2840 | CAAUUCCA | CUGAUGA   | x          | GAA | AAGCGUCU | AGACGCUUU UGGAAUUG |
|    | 2841 | UCAAUUCC | CUGAUGA   | X          | GAA | AAAGCGUC | GACGCUUUU GGAAUUGA |
|    | 2847 | GUCUUGUC | CUGAUGA   | X          | GAA | AUUCCAAA | UUUGGAAUU GACAAGAC |
| 10 | 2863 | UGUUUUGC | CUGAUGA   | X          | GAA | AGUCGCUG | CAGCGACUU GCAAAACA |
|    | 2874 | UUGACGGC | CUGAUGA   | X          | GAA | ACUGUUUU | AAAACAGUA GCCGUCAA |
|    | 2880 | AACAUCUU | CUGAUGA   | x          | GAA | ACGGCUAC | GUAGCCGUC AAGAUGUU |
|    | 2888 | cuucuuuc | CUGAUGA   | X          | GAA | ACAUCUUG | CAAGAUGUU GAAAGAAG |
|    | 2917 | GAGGGCUC | CUGAUGA   | X          | GAA | AUGCUCGC | GCGAGCAUC GAGCCCUC |
| 15 | 2925 | UCAGACAU | CUGAUGA   | X          | GAA | AGGGCUCG | CGAGCCCUC AUGUCUGA |
|    | 2930 | UGAGUUCA | CUGAUGA   | X          | GAA | ACAUGAGG | CCUCAUGUC UGAACUCA |
|    | 2937 | AGGAUCUU | CUGAUGA   | x          | GAA | AGUUCAGA | UCUGAACUC AAGAUCCU |
|    | 2943 | UGGAUGAG | CUGAUGA   | X          | GAA | AUCUUGAG | CUCAAGAUC CUCAUCCA |
|    | 2946 | AUGUGGAU | CUGAUGA   | X          | GAA | AGGAUCUU | AAGAUCCUC AUCCACAU |
| 20 | 2949 | CCAAUGUG | CUGAUGA   | x          | GAA | AUGAGGAU | AUCCUCAUC CACAUUGG |
|    | 2955 | UGGUGACC | CUGAUGA   | x          | GAA | AUGUGGAU | AUCCACAUU GGUCACCA |
|    | 2959 | GAGAUGGU | CUGAUGA   | X          | GAA | ACCAAUGU | ACAUUGGUC ACCAUCUC |
|    | 2965 | CACAUUGA | CUGAUGA   | X          | GAA | AUGGUGAC | GUCACCAUC UCAAUGUG |
|    | 2967 | ACCACAUU | CUGAUGA   | X          | GAA | AGAUGGUG | CACCAUCUC AAUGUGGU |
| 25 | 2982 | GCGCCUAG | CUGAUGA   | X          | GAA | AGGUUCAC | GUGAACCUC CUAGGCGC |
|    | 2985 | CAGGCGCC | CUGAUGA   | X          | GAA | AGGAGGUU | AACCUCCUA GGCGCCUG |
|    | 3013 | CACCAUGA | CUGAUGA   | x          | GAA | AGGCCCUC | GAGGGCCUC UCAUGGUG |
|    | 3015 | AUCACCAU | CUGAUGA   | x          | GAA | AGAGGCCC | GGGCCUCUC AUGGUGAU |
|    | 3024 | AAUUCCAC | CUGAUGA   | x          | GAA | AUCACCAU | AUGGUGAUU GUGGAAUU |
| 30 | 3032 | ACUUGCAG | CUGAUGA   | x          | GAA | AUUCCACA | UGUGGAAUU CUGCAAGU |

|    | 3033 | AACUUGCA   | CUGAUGA | A 3        | GA,   | AAUUCCAC | GUGGAAUUC UGCAAGUU |
|----|------|------------|---------|------------|-------|----------|--------------------|
|    | 3041 | GGUUUCCA   | CUGAUGA | <b>Y</b> 3 | GAZ   | ACUUGCAG | CUGCAAGUU UGGAAACC |
|    | 3042 | AGGUUUCO   | CUGAUGA | χ.         | ( GAA | AACUUGCA | UGCAAGUUU GGAAACCU |
|    | 3051 | . UAAGUUGA | CUGAUGA | X X        | GAA   | AGGUUUCC | GGAAACCUA UCAACUUA |
| 5  | 3053 | AGUAAGUU   | CUGAUGA | X          | GAA   | AUAGGUUU | AAACCUAUC AACUUACU |
|    | 3058 | CCGUAAGU   | CUGAUGA | X.         | GAA   | AGUUGAUA | UAUCAACUU ACUUACGG |
|    | 3059 | CCCGUAAG   | CUGAUGA | Х          | GAA   | AAGUUGAU | AUCAACUUA CUUACGGG |
|    | 3062 | UGCCCCGU   | CUGAUGA | X          | GAA   | AGUAAGUU | AACUUACUU ACGGGGCA |
|    | 3063 | UUGCCCCG   | CUGAUGA | . <b>X</b> | GAA   | AAGUAAGU | ACUUACUUA CGGGGCAA |
| 10 | 3083 | AGGGAACA   | CUGAUGA | X          | GAA   | AUUCAUUU | AAAUGAAUU UGUUCCCU |
|    | 3084 | UAGGGAAC   | CUGAUGA | X          | GAA   | AAUUCAUU | AAUGAAUUU GUUCCCUA |
|    | 3087 | UUAUAGGG   | CUGAUGA | X          | GAA   | ACAAAUUC | GAAUUUGUU CCCUAUAA |
|    | 3088 | CUUAUAGG   | CUGAUGA | X          | GAA   | AACAAAUU | AAUUUGUUC CCUAUAAG |
|    | 3092 | UGCUCUUA   | CUGAUGA | x          | GAA   | AGGGAACA | UGUUCCCUA UAAGAGCA |
| 15 | 3094 | UUUGCUCU   | CUGAUGA | X          | GAA   | AUAGGGAA | UUCCCUAUA AGAGCAAA |
|    | 3113 | CCUGGCGG   | CUGAUGA | X          | GAA   | AGCGUGCC | GGCACGCUU CCGCCAGG |
|    | 3114 | CCCUGGCG   | CUGAUGA | X          | GAA   | AAGCGUGC | GCACGCUUC CGCCAGGG |
|    | 3131 | CCCCAACG   | CUGAUGA | X          | GAA   | AGUCCUUG | CAAGGACUA CGUUGGGG |
|    | 3135 | AGCUCCCC   | CUGAUGA | x          | GAA   | ACGUAGUC | GACUACGUU GGGGAGCU |
| 20 | 3144 | UCCACGGA   | CUGAUGA | X          | GAA   | AGCUCCCC | GGGGAGCUC UCCGUGGA |
|    | 3146 | GAUCCACG   | CUGAUGA | X          | GAA   | AGAGCUCC | GGAGCUCUC CGUGGAUC |
|    | 3154 | UCUUUUCA   | CUGAUGA | X          | GAA   | AUCCACGG | CCGUGGAUC UGAAAAGA |
|    | 3167 | UGCUGUCC   | CUGAUGA | X          | GAA   | AGCGUCUU | AAGACGCUU GGACAGCA |
|    | 3177 | CUGCUGGU   | CUGAUGA | X          | GAA   | AUGCUGUC | GACAGCAUC ACCAGCAG |
| 25 | 3194 | AGCUGGCA   | CUGAUGA | X          | GAA   | AGCUCUGG | CCAGAGCUC UGCCAGCU |
|    | 3203 | CAAAGCCU   | CUGAUGA | x          | GAA   | AGCUGGCA | UGCCAGCUC AGGCUUUG |
|    | 3209 | CCUCAACA   | CUGAUGA | х          | GAA   | AGCCUGAG | CUCAGGCUU UGUUGAGG |
|    | 3210 | UCCUCAAC   | CUGAUGA | x          | GAA   | AAGCCUGA | UCAGGCUUU GUUGAGGA |
|    | 3213 | UUCUCCUC   | CUGAUGA | X          | GAA   | ACAAAGCC | GGCUUUGUU GAGGAGAA |
| 30 | 3224 | CACUGAGC   | CUGAUGA | X          | GAA   | AUUUCUCC | GGAGAAAUC GCUCAGUG |
|    |      |            |         |            |       |          |                    |

PCT/US96/17480

|    | 3228         | ACAUCACU | J CUGAUGA | X | GAA | AGCGAUUU | AAAUCGCUC AGUGAUGU |
|----|--------------|----------|-----------|---|-----|----------|--------------------|
|    | 3237         | טכטטככטכ | CUGAUGA   | X | GAA | ACAUCACU | AGUGAUGUA GAGGAAGA |
|    | 3253         | UUCUUCAG | CUGAUGA   | X | GAA | AGCUUCUU | AAGAAGCUU CUGAAGAA |
|    | 3254         | GUUCUUCA | CUGAUGA   | X | GAA | AAGCUUCU | AGAAGCUUC UGAAGAAC |
| 5  | 3266         | AGUCCUUG | CUGAUGA   | X | GAA | ACAGUUCU | AGAACUGUA CAAGGACU |
|    | 3275         | AGGUCAGG | CUGAUGA   | X | GAA | AGUCCUUG | CAAGGACUU CCUGACCU |
|    | 3276         | AAGGUCAG | CUGAUGA   | x | GAA | AAGUCCUU | AAGGACUUC CUGACCUU |
|    | 3284         | GAUGCUCC | CUGAUGA   | x | GAA | AGGUCAGG | CCUGACCUU GGAGCAUC |
|    | 3292         | ACAGAUGA | CUGAUGA   | X | GAA | AUGCUCCA | UGGAGCAUC UCAUCUGU |
| 10 | 3294         | UAACAGAU | CUGAUGA   | X | GAA | AGAUGCUC | GAGCAUCUC AUCUGUUA |
|    | 3297         | CUGUAACA | CUGAUGA   | x | GAA | AUGAGAUG | CAUCUCAUC UGUUACAG |
|    | 3301         | GAAGCUGU | CUGAUGA   | x | GAA | ACAGAUGA | UCAUCUGUU ACAGCUUC |
|    | 3302         | GGAAGCUG | CUGAUGA   | x | GAA | AACAGAUG | CAUCUGUUA CAGCUUCC |
|    | 3308         | CCACUUGG | CUGAUGA   | x | GAA | AGCUGUAA | UUACAGCUU CCAAGUGG |
| 15 | 3309         | GCCACUUG | CUGAUGA   | x | GAA | AAGCUGUA | UACAGCUUC CAAGUGGC |
|    | 3319         | CAUGCCCU | CUGAUGA   | x | GAA | AGCCACUU | AAGUGGCUA AGGGCAUG |
|    | 3332         | AUGCCAAG | CUGAUGA   | X | GAA | ACUCCAUG | CAUGGAGUU CUUGGCAU |
|    | 3333         | GAUGCCAA | CUGAUGA   | X | GAA | AACUCCAU | AUGGAGUUC UUGGCAUC |
|    | 3335         | UUGAUGCC | CUGAUGA   | x | GAA | AGAACUCC | GGAGUUCUU GGCAUCAA |
| 20 | 3341         | ACUUCCUU | CUGAUGA   | X | GAA | AUGCCAAG | CUUGGCAUC AAGGAAGU |
|    | <b>3</b> 352 | CCUGUGGA | CUGAUGA   | x | GAA | ACACUUCC | GGAAGUGUA UCCACAGG |
|    | 3354         | UCCCUGUG | CUGAUGA   | x | GAA | AUACACUU | AAGUGUAUC CACAGGGA |
|    | 3381         | GAUAGGAG | CUGAUGA   | X | GAA | AUGUUUCG | CGAAACAUU CUCCUAUC |
|    | 3382         | CGAUAGGA | CUGAUGA   | X | GAA | AAUGUUUC | GAAACAUUC UCCUAUCG |
| 25 | 3384         | UCCGAUAG | CUGAUGA   | x | GAA | AGAAUGUU | AACAUUCUC CUAUCGGA |
|    | 3387         | UUCUCCGA | CUGAUGA   | X | GAA | AGGAGAAU | AUUCUCCUA UCGGAGAA |
|    | 3389         | UCUUCUCC | CUGAUGA   | X | GAA | AUAGGAGA | UCUCCUAUC GGAGAAGA |
|    | 3405         | CAGAUCUU | CUGAUGA   | X | GAA | ACCACAUU | AAUGUGGUU AAGAUCUG |
|    | 3406         | ACAGAUCU | CUGAUGA   | X | GAA | AACCACAU | AUGUGGUUA AGAUCUGU |
| 30 | 3411         | AAGUCACA | CUGAUGA   | x | GAA | AUCUUAAC | GUUAAGAUC UGUGACUU |

|     | 3419 CCAAGCCG CUGAUGA X GAA AGUCACAG | CUGUGACUU CGGCUUGG |
|-----|--------------------------------------|--------------------|
|     | 3420 GCCAAGCC CUGAUGA X GAA AAGUCACA |                    |
|     | 3425 CCCGGGCC CUGAUGA X GAA AGCCGAAG |                    |
|     | 3438 UCUUUAUA CUGAUGA X GAA AUGUCCCG |                    |
| 5   | 3439 GUCUUUAU CUGAUGA X GAA AAUGUCCC |                    |
|     | 3440 GGUCUUUA CUGAUGA X GAA AAAUGUCC |                    |
|     | 3442 CGGGUCUU CUGAUGA X GAA AUAAAUGU |                    |
|     | 3454 UCUGACAU CUGAUGA X GAA AUCCGGGU | ACCCGGAUU AUGUCAGA |
|     | 3455 UUCUGACA CUGAUGA X GAA AAUCCGGG | CCCGGAUUA UGUCAGAA |
| 10  | 3459 CCUUUUCU CUGAUGA X GAA ACAUAAUC | GAUUAUGUC AGAAAAGG |
|     | 3480 UUCAAAGG CUGAUGA X GAA AGUCGGGC | GCCCGACUC CCUUUGAA |
|     | 3484 CCACUUCA CUGAUGA X GAA AGGGAGUC | GACUCCCUU UGAAGUGG |
|     | 3485 UCCACUUC CUGAUGA X GAA AAGGGAGU | ACUCCCUUU GAAGUGGA |
|     | 3510 CUGUCAAA CUGAUGA X GAA AUGGUUUC | GAAACCAUU UUUGACAG |
| 15  | 3511 UCUGUCAA CUGAUGA X GAA AAUGGUUU | AAACCAUUU UUGACAGA |
|     | 3512 CUCUGUCA CUGAUGA X GAA AAAUGGUU | AACCAUUUU UGACAGAG |
|     | 3513 ACUCUGUC CUGAUGA X GAA AAAAUGGU | ACCAUUUUU GACAGAGU |
|     | 3522 AUUGUGUA CUGAUGA X GAA ACUCUGUC | GACAGAGUA UACACAAU |
|     | 3524 GAAUUGUG CUGAUGA X GAA AUACUCUG | CAGAGUAUA CACAAUUC |
| 20  | 3531 UCGCUCUG CUGAUGA X GAA AUUGUGUA | UACACAAUU CAGAGCGA |
|     | 3532 AUCGCUCU CUGAUGA X GAA AAUUGUGU | ACACAAUUC AGAGCGAU |
|     | 3548 CACCGAAA CUGAUGA X GAA ACCACACA | UGUGUGGUC UUUCGGUG |
|     | 3550 CACACCGA CUGAUGA X GAA AGACCACA | UGUGGUCUU UCGGUGUG |
|     | 3551 ACACACCG CUGAUGA X GAA AAGACCAC | GUGGUCUUU CGGUGUGU |
| 25  | 3552 AACACACC CUGAUGA X GAA AAAGACCA | UGGUCUUUC GGUGUGUU |
|     | 3560 CCCAGAGC CUGAUGA X GAA ACACACCG | CGGUGUGUU GCUCUGGG |
|     | 3564 AUUUCCCA CUGAUGA X GAA AGCAACAC | GUGUUGCUC UGGGAAAU |
|     | 3573 AAGGAAAA CUGAUGA X GAA AUUUCCCA | UGGGAAAUA UUUUCCUU |
| 3.0 | 3575 CUAAGGAA CUGAUGA X GAA AUAUUUCC | GGAAAUAUU UUCCUUAG |
| 30  | 3576 CCUAAGGA CUGAUGA X GAA AAUAUUUC | GAAAUAUUU UCCUUAGG |
|     |                                      |                    |

|    | 3577 ACCUA  | AGG CUGAUG  | A Z        | K GAZ | UUUAUAAA A  | AAAUAUUUU CCUUAGGU |
|----|-------------|-------------|------------|-------|-------------|--------------------|
|    | 3578 CACCU  | AAG CUGAUG  | (A         | ( GAA | UUAUAAAAA A | AAUAUUUUC CUUAGGUG |
|    | 3581 AGGCA  | CCU CUGAUG  | A 3        | GAA   | AGGAAAAU    | AUUUUCCUU AGGUGCCU |
|    | 3582 GAGGC  | ACC CUGAUG  | A )        | GAA   | AAGGAAAA    | UUUUCCUUA GGUGCCUC |
| 5  | 3590 GGUAU  | GGG CUGAUG  | A X        | GAA   | AGGCACCU    | AGGUGCCUC CCCAUACC |
|    | 3596 CCCCA  | GGG CUGAUG  | K A        | GAA   | AUGGGGAG    | CUCCCCAUA CCCUGGGG |
|    | 3606 UCAAU  | CUU CUGAUG  | АХ         | GAA   | ACCCCAGG    | CCUGGGGUC AAGAUUGA |
|    | 3612 UCUUC  | AUC CUGAUG  | АХ         | GAA   | AUCUUGAC    | GUCAAGAUU GAUGAAGA |
|    | 3623 UCCUA  | CAA CUGAUG  | АХ         | GAA   | AUUCUUCA    | UGAAGAAUU UUGUAGGA |
| 10 | 3624 CUCCU  | ACA CUGAUG  | АХ         | GAA   | AAUUCUUC    | GAAGAAUUU UGUAGGAG |
|    | 3625 UCUCCT | UAC CUGAUG. | X A        | GAA   | AAAUUCUU    | AAGAAUUUU GUAGGAGA |
|    | 3628 CAAUCT | UCC CUGAUG  | A X        | GAA   | ACAAAAUU    | AAUUUUGUA GGAGAUUG |
|    | 3635 CUUCUT | JUC CUGAUG  | A X        | GAA   | AUCUCCUA    | UAGGAGAUU GAAAGAAG |
|    | 3649 CCGCAU | JUC CUGAUG  | A X        | GAA   | AGUUCCUU    | AAGGAACUA GAAUGCGG |
| 15 | 3661 GUAGUC | CAG CUGAUG  | X A        | GAA   | AGCCCGCA    | UGCGGGCUC CUGACUAC |
|    | 3668 GGGUAG | GUG CUGAUG  | A X        | GAA   | AGUCAGGA    | UCCUGACUA CACUACCC |
|    | 3673 UUCUGG | GG CUGAUG   | X          | GAA   | AGUGUAGU    | ACUACACUA CCCCAGAA |
|    | 3686 UGGUCU | IGG CUGAUGA | x          | GAA   | ACAUUUCU    | AGAAAUGUA CCAGACCA |
|    | 3734 CUGAAA | AC CUGAUGA  | X          | GAA   | AGGGUCUC    | GAGACCCUC GUUUUCAG |
| 20 | 3737 ACUCUG | AA CUGAUGA  | X          | GAA   | ACGAGGGU    | ACCCUCGUU UUCAGAGU |
|    | 3738 AACUCU | IGA CUGAUGA | x          | GAA   | AACGAGGG    | CCCUCGUUU UCAGAGUU |
|    | 3739 CAACUC | UG CUGAUGA  | X          | GAA   | AAACGAGG    | CCUCGUUUU CAGAGUUG |
|    | 3740 CCAACU | CU CUGAUGA  | X          | GAA   | AAAACGAG    | CUCGUUUUC AGAGUUGG |
|    | 3746 GCUCCA | .CC CUGAUGA | X          | GAA   | ACUCUGAA    | UUCAGAGUU GGUGGAGC |
| 25 | 3757 GUUUCC | CA CUGAUGA  | X          | GAA   | AUGCUCCA    | UGGAGCAUU UGGGAAAC |
|    | 3758 GGUUUC | CC CUGAUGA  | X          | GAA   | AAUGCUCC    | GGAGCAUUU GGGAAACC |
|    | 3768 GCUUGC | AG CUGAUGA  | . x        | GAA   | AGGUUUCC    | GGAAACCUC CUGCAAGC |
|    | 3803 GAACAA | UA CUGAUGA  | X          | GAA   | AGUCUUUG    | CAAAGACUA UAUUGUUC |
|    | 3805 AAGAAC | AA CUGAUGA  | X          | GAA   | AUAGUCUU    | AAGACUAUA UUGUUCUU |
| 30 | 3807 GGAAGA | AC CUGAUGA  | . <b>x</b> | GAA   | AUAUAGUC    | GACUAUAUU GUUCUUCC |

|    | 3810 | AUUGGAA    | G CUGAUGA | X X | GA. | A ACAAUAUA | UAUAUUGUU   | CUUCCAAU |
|----|------|------------|-----------|-----|-----|------------|-------------|----------|
|    | 3811 | CAUUGGA    | A CUGAUGA | X A | GAA | AACAAUAU   | AUAUUGUUC   | UUCCAAUG |
|    | 3813 | GACAUUGO   | CUGAUGA   | X   | GAA | AGAACAAU   | AUUGUUCUU   | CCAAUGUC |
|    | 3814 | UGACAUUG   | CUGAUGA   | X   | GAA | AAGAACAA   | UUGUUCUUC   | CAAUGUCA |
| 5  | 3821 | . gugucucu | J CUGAUGA | X   | GAA | ACAUUGGA   |             |          |
|    | 3847 | GAGUCCAG   | CUGAUGA   | x   | GAA | AUCCUCUU   | AAGAGGAUU   | CUGGACUC |
|    | 3848 | AGAGUCCA   | CUGAUGA   | . х | GAA | AAUCCUCU   | AGAGGAUUC   | UGGACUCU |
| -  | 3855 | GGCAGGGA   | CUGAUGA   | X   | GAA | AGUCCAGA   | UCUGGACUC   | UCCCUGCC |
|    | 3857 | UAGGCAGG   | CUGAUGA   | X   | GAA | AGAGUCCA   | UGGACUCUC   | CCUGCCUA |
| 10 | 3865 | AGGUGAGG   | CUGAUGA   | X   | GAA | AGGCAGGG   | CCCUGCCUA   | CCUCACCU |
|    | 3869 | AAACAGGU   | CUGAUGA   | x   | GAA | AGGUAGGC   | GCCUACCUC   | ACCUGUUU |
|    | 3876 | AUACAGGA   | CUGAUGA   | X   | GAA | ACAGGUGA   | UCACCUGUU   | UCCUGUAU |
|    | 3877 | CAUACAGG   | CUGAUGA   | x   | GAA | AACAGGUG   | CACCUGUUU   | CCUGUAUG |
|    | 3878 | CCAUACAG   | CUGAUGA   | X   | GAA | AAACAGGU   | ACCUGUUUC   | CUGUAUGG |
| 15 | -883 | UUCCUCCA   | CUGAUGA   | x   | GAA | ACAGGAAA   | UUUCCUGUA   | UGGAGGAA |
|    | 3914 | CAUAAUGG   | CUGAUGA   | X   | GAA | AUUUGGGG   | CCCCAAAUU   | CCAUUAUG |
|    | 3915 | UCAUAAUG   | CUGAUGA   | X   | GAA | AAUUUGGG   | CCCAAAUUC   | CAUUAUGA |
|    | 3919 | GUUGUCAU   | CUGAUGA   | X   | GAA | AUGGAAUU   | AAUUCCAUU   | AUGACAAC |
|    | 3920 | UGUUGUCA   | CUGAUGA   | x   | GAA | AAUGGAAU   | AUUCCAUUA   | UGACAACA |
| 20 |      | UAAUGACU   |           |     |     |            | GCAGGAAUC   | AGUCAUUA |
|    |      | GAGAUAAU   |           |     |     |            | GAAUCAGUC   | AUUAUCUC |
|    |      | CUGGAGAU   |           |     |     |            | UCAGUCAUU   | AUCUCCAG |
|    |      | UCUGGAGA   |           |     |     |            | CAGUCAUUA   | UCUCCAGA |
|    | 3949 | GUUCUGGA   | CUGAUGA   | x   | GAA | AUAAUGAC   | GUCAUUAUC   | UCCAGAAC |
| 25 | 3951 | CUGUUCUG   | CUGAUGA   | x   | GAA | AGAUAAUG   | CAUUAUCUC   | CAGAACAG |
|    | 3961 | CUUUCGCU   | CUGAUGA   | X   | GAA | ACUGUUCU   | AGAACAGUA   | AGCGAAAG |
|    | 3987 | AAUGUUUU   | CUGAUGA   | X   | GAA | ACACUCAC   | GUGAGUGUA . | AAAACAUU |
|    | 3995 | UAUCUUCA   | CUGAUGA   | X   | GAA | AUGUUUUU   | AAAAACAUU   | UGAAGAUA |
|    | 3996 | AUAUCUUC   | CUGAUGA   | x   | GAA | AAUGUUUU   | AAAACAUUU   | GAAGAUAU |
| 30 | 4003 | CAAUGGGA   | CUGAUGA   | X   | GAA | AUCUUCAA   | UUGAAGAUA   | UCCCAUUG |
|    |      |            |           |     |     |            |             |          |

|    | 4005   | UCCAAUGG | CUGAUGA | X | GAA | AUAUCUUC | GAAGAUAUC CCAUUGGA |
|----|--------|----------|---------|---|-----|----------|--------------------|
|    | 4010   | GUUCCUCO | CUGAUGA | X | GAA | AUGGGAUA | UAUCCCAUU GGAGGAAC |
|    | 4026   | AUCACUUU | CUGAUGA | x | GAA | ACUUCUGG | CCAGAAGUA AAAGUGAU |
|    | 4035   | UCAUCUGG | CUGAUGA | X | GAA | AUCACUUU | AAAGUGAUC CCAGAUGA |
| 5  | 4068   | GAUGCAAG | CUGAUGA | x | GAA | ACCAUCCC | GGGAUGGUC CUUGCAUC |
|    | 4071   | UCUGAUGC | CUGAUGA | x | GAA | AGGACCAU | AUGGUCCUU GCAUCAGA |
|    | 4076   | GCUCUUCU | CUGAUGA | x | GAA | AUGCAAGG | CCUUGCAUC AGAAGAGC |
|    | 4093   | GUCUUCCA | CUGAUGA | x | GAA | AGUUUUCA | UGAAAACUC UGGAAGAC |
|    | 4112   | AUGGAGAU | CUGAUGA | x | GAA | AUUUGUUC | GAACAAAUU AUCUCCAU |
| 10 | 4113   | GAUGGAGA | CUGAUGA | X | GAA | AAUUUGUU | AACAAAUUA UCUCCAUC |
|    | 4115   | aagaugga | CUGAUGA | x | GAA | AUAAUUUG | CAAAUUAUC UCCAUCUU |
|    | 4117   | AAAAGAUG | CUGAUGA | x | GAA | AGAUAAUU | AAUUAUCUC CAUCUUUU |
|    | 4121   | CACCAAAA | CUGAUGA | x | GAA | AUGGAGAU | AUCUCCAUC UUUUGGUG |
|    | 4123   | UCCACCAA | CUGAUGA | x | GAA | AGAUGGAG | CUCCAUCUU UUGGUGGA |
| 15 | 4124   | JUCCACCA | CUGAUGA | x | GAA | AAGAUGGA | UCCAUCUUU UGGUGJAA |
|    | 4125 7 | AUUCCACC | CUGAUGA | x | GAA | AAAGAUGG | CCAUCUUUU GGUGGAAU |
|    | 4144   | CCUGCUUU | CUGAUGA | x | GAA | ACUGGGCA | UGCCCAGUA AAAGCAGG |
|    | 4157 A | AGGCCACA | CUGAUGA | x | GAA | ACUCCCUG | CAGGGAGUC UGUGGCCU |
|    | 4166 A | AGCCUUCC | CUGAUGA | x | GAA | AGGCCACA | UGUGGCCUC GGAAGGCU |
| 20 | 4175 t | CUGGUUG  | CUGAUGA | x | GAA | AGCCUUCC | GGAAGGCUC CAACCAGA |
|    | 4193 0 | CAGACUGG | CUGAUGA | x | GAA | AGCCACUG | CAGUGGCUA CCAGUCUG |
|    | 4199 0 | AUACCCA  | CUGAUGA | x | GAA | ACUGGUAG | CUACCAGUC UGGGUAUC |
|    | 4205 C | UGAGUGA  | CUGAUGA | X | GAA | ACCCAGAC | GUCUGGGUA UCACUCAG |
|    | 4207 A | UCUGAGU  | CUGAUGA | X | GAA | AUACCCAG | CUGGGUAUC ACUCAGAU |
| 25 | 4211 U | GUCAUCU  | CUGAUGA | X | GAA | AGUGAUAC | GUAUCACUC AGAUGACA |
|    | 4235 C | GCUGGAG  | CUGAUGA | X | GAA | ACACGGUG | CACCGUGUA CUCCAGCG |
|    | 4238 C | GUCGCUG  | CUGAUGA | X | GAA | AGUACACG | CGUGUACUC CAGCGACG |
|    | 4257 A | UCUUUAA  | CUGAUGA | X | GAA | AGUCCUGC | GCAGGACUU UUAAAGAU |
|    | 4258 C | AUCUUUA  | CUGAUGA | X | GAA | AAGUCCUG | CAGGACUUU UAAAGAUG |
| 30 | 4259 C | CAUCUUU  | CUGAUGA | X | GAA | AAAGUCCU | AGGACUUUU AAAGAUGG |

|    | 4260 | ACCAUCUU | CUGAUGA | . X | GAA | AAAAGUCC | GGACUUUUA AAGAUGGU |
|----|------|----------|---------|-----|-----|----------|--------------------|
|    | 4281 | UCAGCGUG | CUGAUGA | . X | GAA | ACUGCAGC | GCUGCAGUU CACGCUGA |
|    | 4282 | GUCAGCGU | CUGAUGA | . x | GAA | AACUGCAG | CUGCAGUUC ACGCUGAC |
|    | 4292 | UGGUCCCU | CUGAUGA | X   | GAA | AGUCAGCG | CGCUGACUC AGGGACCA |
| 5  | 4311 | CAGGAGGU | CUGAUGA | X   | GAA | AGCUGCAG | CUGCAGCUC ACCUCCUG |
|    | 4316 | UUAAACAG | CUGAUGA | X   | GAA | AGGUGAGC | GCUCACCUC CUGUUUAA |
|    | 4321 | UCCAUUUA | CUGAUGA | X   | GAA | ACAGGAGG | CCUCCUGUU UAAAUGGA |
|    | 4322 | UUCCAUUU | CUGAUGA | X   | GAA | AACAGGAG | CUCCUGUUU AAAUGGAA |
|    | 4323 | CUUCCAUU | CUGAUGA | X   | GAA | AAACAGGA | UCCUGUUUA AAUGGAAG |
| 10 | 4336 | CGGGACAG | CUGAUGA | X   | GAA | ACCACUUC | GAAGUGGUC CUGUCCCG |
|    | 4341 | GGAGCCGG | CUGAUGA | X   | GAA | ACAGGACC | GGUCCUGUC CCGGCUCC |
|    | 4348 | UGGGGGCG | CUGAUGA | X   | GAA | AGCCGGGA | UCCCGGCUC CGCCCCCA |
|    | 4360 | AUUUCCAG | CUGAUGA | x   | GAA | AGUUGGGG | CCCCAACUC CUGGAAAU |
|    | 4369 | UCUCUCGU | CUGAUGA | X   | GAA | AUUUCCAG | CUGGAAAUC ACGAGAGA |
| 15 | 4387 | GAAAAUCU | CUGAUGA | x   | GAA | AGCAGCAC | GUGCUGCUU AGAUUUUC |
|    | 4388 | UGAAAAUC | CUGAUGA | X   | GAA | AAGCAGCA | UGCUGCUUA GAUUUUCA |
|    | 4392 | CACUUGAA | CUGAUGA | X   | GAA | AUCUAAGC | GCUUAGAUU UUCAAGUG |
|    | 4393 | ACACUUGA | CUGAUGA | x   | GAA | AAUCUAAG | CUUAGAUUU UCAAGUGU |
|    | 4394 | AACACUUG | CUGAUGA | X   | GAA | AAAUCUAA | UUAGAUUUU CAAGUGUU |
| 20 | 4395 | CAACACUU | CUGAUGA | X   | GAA | AAAAUCUA | UAGAUUUUC AAGUGUUG |
|    | 4402 | GAAAGAAC | CUGAUGA | X   | GAA | ACACUUGA | UCAAGUGUU GUUCUUUC |
|    | 4405 | GUGGAAAG | CUGAUGA | X   | GAA | ACAACACU | AGUGUUGUU CUUUCCAC |
|    | 4406 | GGUGGAAA | CUGAUGA | X   | GAA | AACAACAC | GUGUUGUUC UUUCCACC |
|    | 4408 | GUGGUGGA | CUGAUGA | X   | GAA | AGAACAAC | GUUGUUCUU UCCACCAC |
| 25 | 4409 | GGUGGUGG | CUGAUGA | X   | GAA | AAGAACAA | UUGUUCUUU CCACCACC |
|    | 4410 | GGGUGGUG | CUGAUGA | X   | GAA | AAAGAACA | UGUUCUUUC CACCACCC |
|    | 4425 | AAUGUGGC | CUGAUGA | X   | GAA | ACUUCCGG | CCGGAAGUA GCCACAUU |
|    | 4433 | GAAAAUCA | CUGAUGA | X   | GAA | AUGUGGCU | AGCCACAUU UGAUUUUC |
|    | 4434 | UGAAAAUC | CUGAUGA | X   | GAA | AAUGUGGC | GCCACAUUU GAUUUUCA |
| 30 | 4438 | AAAAUGAA | CUGAUGA | X   | GAA | AUCAAAUG | CAUUUGAUU UUCAUUUU |

PCT/US96/17480

|    | 4439   | AAAAAUGA | CUGAUGA | X | GAA | AAUCAAAU | AUUUGAUUU | UCAUUUUU |
|----|--------|----------|---------|---|-----|----------|-----------|----------|
|    | 4440   | CAAAAAUG | CUGAUGA | X | GAA | AAAUCAAA | UUUGAUUUU | CAUUUUUG |
|    | 4441   | CCAAAAAU | CUGAUGA | X | GAA | AAAAUCAA | UUGAUUUUC | AUUUUUGG |
|    | 4444   | CCUCCAAA | CUGAUGA | X | GAA | AUGAAAAU | AUUUUCAUU | UUUGGAGG |
| 5  | 4445   | UCCUCCAA | CUGAUGA | X | GAA | AAUGAAAA | UUUUCAUUU | UUGGAGGA |
|    | 4446   | CUCCUCCA | CUGAUGA | X | GAA | AAAUGAAA | UUUCAUUUU | UGGAGGAG |
|    | 4447   | CCUCCUCC | CUGAUGA | X | GAA | AAAAUGAA | UUCAUUUUU | GGAGGAGG |
|    | 4461   | UGCAGUCU | CUGAUGA | X | GAA | AGGUCCCU | AGGGACCUC | AGACUGCA |
|    | 4477   | CUGAGGAC | CUGAUGA | X | GAA | AGCUCCUU | AAGGAGCUU | GUCCUCAG |
| 10 | 4480   | GCCCUGAG | CUGAUGA | x | GAA | ACAAGCUC | GAGCUUGUC | CUCAGGGC |
|    | 4483   | AAUGCCCU | CUGAUGA | x | GAA | AGGACAAG | CUUGUCCUC | AGGGCAUU |
|    | 4491   | UCUCUGGA | CUGAUGA | X | GAA | AUGCCCUG | CAGGGCAUU | UCCAGAGA |
|    | 4492   | UUCUCUGG | CUGAUGA | X | GAA | AAUGCCCU | AGGGCAUUU | CCAGAGAA |
|    | 4493   | CUUCUCUG | CUGAUGA | X | GAA | AAAUGCCC | GGGCAUUUC | CAGAGAAG |
| 15 | 4525   | GUAGAGUC | CUGAUGA | X | GAA | ACACAUUC | GAAUGUGUU | GACUCUAC |
|    | 4530   | AGAGAGUA | CUGAUGA | X | GAA | AGUCAACA | UGUUGACUC | UACUCUCU |
|    | 4532   | AAAGAGAG | CUGAUGA | X | GAA | AGAGUCAA | UUGACUCUA | CUCUCUUU |
|    | 4535   | GGAAAAGA | CUGAUGA | X | GAA | AGUAGAGU | ACUCUACUC | UCUUUUCC |
|    | 4537   | AUGGAAAA | CUGAUGA | X | GAA | AGAGUAGA | UCUACUCUC | UUUUCCAU |
| 20 | 4539 ( | GAAUGGAA | CUGAUGA | X | GAA | AGAGAGUA | UACUCUCUU | UUCCAUUC |
|    | 4540   | UGAAUGGA | CUGAUGA | X | GAA | AAGAGAGU | ACUCUCUUU | UCCAUUCA |
|    | 4541 2 | AUGAAUGG | CUGAUGA | X | GAA | AAAGAGAG | cucucuuuu | CCAUUCAU |
|    | 4542   | AAUGAAUG | CUGAUGA | X | GAA | AAAAGAGA | UCUCUUUUC | CAUUCAUU |
|    | 4546 T | UUUAAAUG | CUGAUGA | X | GAA | AUGGAAAA | UUUUCCAUU | CAUUUAAA |
| 25 | 4547   | UAAAUUUU | CUGAUGA | X | GAA | AAUGGAAA | UUUCCAUUC | AUUUAAAA |
|    | 4550 ( | GACUUUUA | CUGAUGA | X | GAA | AUGAAUGG | CCAUUCAUU | UAAAAGUC |
|    | 4551 ( | GGACUUUU | CUGAUGA | X | GAA | AAUGAAUG | CAUUCAUUU | AAAAGUCC |
|    | 4552   | AGGACUUU | CUGAUGA | X | GAA | AAAUGAAU | AUUCAUUUA | AAAGUCCU |
|    | 4558 T | JUAUAUAG | CUGAUGA | X | GAA | ACUUUUAA | UUAAAAGUC | CUAUAUAA |
| 30 | 4561 / | ACAUUAUA | CUGAUGA | X | GAA | AGGACUUU | AAAGUCCUA | UAUAAUGU |

|    | 456  | 3 GCACAUU | A CUGAUG  | Α          | X GA | A AUAGGACU | AGUCCUAUA UAAUGUG  |
|----|------|-----------|-----------|------------|------|------------|--------------------|
|    | 456  | 5 GGGCACA | U CUGAUG  | A          | X GA | A AUAUAGGA | UCCUAUAUA AUGUGCCO |
|    | 458  | 3 GGUAGUG | A CUGAUG  | Α          | X GA | A ACCACAGO |                    |
|    | 458  | 5 CUGGUAG | U CUGAUG  | A          | X GA | A AGACCACA |                    |
| 5  | 458  | 9 UUAACUG | G CUGAUG  | A :        | X GA | A AGUGAGAC |                    |
|    | 459  | 5 UUUGCUU | U CUGAUG  | <b>A</b> : | X GA | A ACUGGUAG |                    |
|    | 4596 | S UUUUGCU | U CUGAUG  | A :        | X GA | A AACUGGUA |                    |
|    | 4609 | GUGUUUG   | A CUGAUG  | A :        | K GA | A AGUCUUUU |                    |
|    | 4610 | CGUGUUU   | G CUGAUG  | A 2        | K GA | A AAGUCUUU |                    |
| 10 | 4611 | ACGUGUUT  | J CUGAUGA | A )        | GA,  | AAAGUCUU   |                    |
|    | 4625 | GGAGGAC   | CUGAUGA   | <b>A</b> > | GA2  | AGUCCACG   |                    |
|    | 4629 | UCUUGGA   | CUGAUG    | K A        | GAZ  | ACAGAGUC   | GACUCUGUC CUCCAAGA |
|    | 4632 | ACUUCUUC  | CUGAUGA   | X A        | GAA  | AGGACAGA   | UCUGUCCUC CAAGAAGU |
|    | 4654 | GUUUCACA  | CUGAUGA   | Х          | GAA  | AGGUGCCG   |                    |
| 15 | 4668 | GCCCAUUC  | CUGAUGA   | X          | GAA  | AUCCAGUU   | AACUGGAUC GAAUGGGC |
|    | 4683 | AACACACA  | CUGAUGA   | X          | GAA  | AGCAUUGC   | GCAAUGCUU UGUGUGUU |
|    | 4684 | CAACACAC  | CUGAUGA   | X          | GAA  | AAGCAUUG   | CAAUGCUUU GUGUGUUG |
|    | 4691 | CCAUCCUC  | CUGAUGA   | x          | GAA  | ACACACAA   | UUGUGUGUU GAGGAUGG |
|    | 4709 | GGCCCUGG  | CUGAUGA   | X          | GAA  | ACAUCUCA   | UGAGAUGUC CCAGGGCC |
| 20 | 4722 | GGUAGACA  | CUGAUGA   | x          | GAA  | ACUCGGCC   | GGCCGAGUC UGUCUACC |
|    | 4726 | CCAAGGUA  | CUGAUGA   | x          | GAA  | ACAGACUC   | GAGUCUGUC UACCUUGG |
|    | 4728 | CUCCAAGG  | CUGAUGA   | x          | GAA  | AGACAGAC   | GUCUGUCUA CCUUGGAG |
|    | 4732 | AAGCCUCC  | CUGAUGA   | x          | GAA  | AGGUAGAC   | GUCUACCUU GGAGGCUU |
|    | 4740 | CCUCCACA  | CUGAUGA   | x          | GAA  | AGCCUCCA   | UGGAGGCUU UGUGGAGG |
| 25 | 4741 | UCCUCCAC  | CUGAUGA   | x          | GAA  | AAGCCUCC   | GGAGGCUUU GUGGAGGA |
|    | 4758 | UUGGCUCA  | CUGAUGA   | x          | GAA  | AGCCCGCA   | UGCGGGCUA UGAGCCAA |
|    |      |           |           |            |      |            | CCAAGUGUU AAGUGUGG |
|    | 4772 | CCCACACU  | CUGAUGA   | X          | GAA  | AACACUUG   | CAAGUGUUA AGUGUGGG |
|    | 4811 | CUCCGAGC  | CUGAUGA   | x          | GAA  | ACUUGCGC   | GCGCAAGUC GCUCGGAG |
| 30 | 4815 | CGCUCUCC  | CUGAUGA   | x          | GAA  | AGCGACUU   | AAGUCGCUC GGAGAGCG |

|    | 4826 | CAGGCUCC | CUGAUGA | X          | GAA | ACCGCUCU | AGAGCGGUU GGAGCCUG |
|----|------|----------|---------|------------|-----|----------|--------------------|
|    | 4844 | GCCAGCAC | CUGAUGA | X          | GAA | AUGCAUCU | AGAUGCAUU GUGCUGGC |
|    | 4854 | CUCCACCA | CUGAUGA | . <b>x</b> | GAA | AGCCAGCA | UGCUGGCUC UGGUGGAG |
|    | 4870 | CAGGCCAC | CUGAUGA | X          | GAA | AGCCCACC | GGUGGGCUU GUGGCCUG |
| 5  | 4880 | CGUUUCCU | CUGAUGA | X          | GAA | ACAGGCCA | UGGCCUGUC AGGAAACG |
|    | 4908 | CAAAACCA | CUGAUGA | X          | GAA | ACCCUGCC | GGCAGGGUU UGGUUUUG |
|    | 4909 | CCAAAACC | CUGAUGA | X          | GAA | AACCCUGC | GCAGGGUUU GGUUUUGG |
|    | 4913 | CCUUCCAA | CUGAUGA | X          | GAA | ACCAAACC | GGUUUGGUU UUGGAAGG |
|    | 4914 | ACCUUCCA | CUGAUGA | X          | GAA | AACCAAAC | GUUUGGUUU UGGAAGGU |
| 10 | 4915 | AACCUUCC | CUGAUGA | X          | GAA | AAACCAAA | UUUGGUUUU GGAAGGUU |
|    | 4923 | AGCACGCA | CUGAUGA | X          | GAA | ACCUUCCA | UGGAAGGUU UGCGUGCU |
|    | 4924 | GAGCACGC | CUGAUGA | X          | GAA | AACCUUCC | GGAAGGUUU GCGUGCUC |
|    | 4932 | ACUGUGAA | CUGAUGA | X          | GAA | AGCACGCA | UGCGUGCUC UUCACAGU |
|    | 4934 | CGACUGUG | CUGAUGA | x          | GAA | AGAGCACG | CGUGCUCUU CACAGUCG |
| 15 | 4935 | CCGACUGU | CUGAUGA | X          | GAA | AAGAGCAC | GUGCUCUUC ACAGUCGG |
|    | 4941 | UGUAACCC | CUGAUGA | X          | GAA | ACUGUGAA | UUCACAGUC GGGUUACA |
|    | 4946 | UCGCCUGU | CUGAUGA | X          | GAA | ACCCGACU | AGUCGGGUU ACAGGCGA |
|    | 4947 | CUCGCCUG | CUGAUGA | X          | GAA | AACCCGAC | GUCGGGUUA CAGGCGAG |
|    | 4957 | CCACAGGG | CUGAUGA | X          | GAA | ACUCGCCU | AGGCGAGUU CCCUGUGG |
| 20 | 4958 | GCCACAGG | CUGAUGA | X          | GAA | AACUCGCC | GGCGAGUUC CCUGUGGC |
|    | 4969 | GAGUAGGA | CUGAUGA | X          | GAA | ACGCCACA | UGUGGCGUU UCCUACUC |
|    |      | GGAGUAGG |         |            |     |          | GUGGCGUUU CCUACUCC |
|    |      | AGGAGUAG |         |            |     |          | UGGCGUUUC CUACUCCU |
|    | 4974 | AUUAGGAG | CUGAUGA | X          | GAA | AGGAAACG | CGUUUCCUA CUCCUAAU |
| 25 | 4977 | CUCAUUAG | CUGAUGA | X          | GAA | AGUAGGAA | UUCCUACUC CUAAUGAG |
|    |      | ACUCUCAU |         |            |     |          | CUACUCCUA AUGAGAGU |
|    |      | CCGGAAGG |         |            |     |          | AUGAGAGUU CCUUCCGG |
|    |      | UCCGGAAG |         |            |     |          | UGAGAGUUC CUUCCGGA |
|    |      | GAGUCCGG |         |            |     |          | GAGUUCCUU CCGGACUC |
| 30 | 4994 | AGAGUCCG | CUGAUGA | X          | GAA | AAGGAACU | AGUUCCUUC CGGACUCU |

|      | 5001 ACACGUAA CUGAUGA X GAA AGUCCGO  | A UCCGGACUC UUACGUGU   |
|------|--------------------------------------|--|
|      | 5003 AGACACGU CUGAUGA X GAA AGAGUCO  |  |
|      | 5004 GAGACACG CUGAUGA X GAA AAGAGUC  |  |
|      | 5010 GGCCAGGA CUGAUGA X GAA ACACGUA  |  |
| 5    | 5012 CAGGCCAG CUGAUGA X GAA AGACACG  |  |
|      | 5046 GAAGGAGC CUGAUGA X GAA AGCUGCA  | U AUGCAGCUU GCUCCUUC   |
|      | 5050 UGAGGAAG CUGAUGA X GAA AGCAAGC  | U AGCUUGCUC CUUCCUCA   |
|      | 5053 AGAUGAGG CUGAUGA X GAA AGGAGCA  |  |
|      | 5054 GAGAUGAG CUGAUGA X GAA AAGGAGC  | A UGCUCCUUC CUCAUCUC   |
| 10   | 5057 UGAGAGAU CUGAUGA X GAA AGGAAGGA |  |
|      | 5060 GCCUGAGA CUGAUGA X GAA AUGAGGAX |  |
|      | 5062 CAGCCUGA CUGAUGA X GAA AGAUGAGO | CCUCAUCUC UCAGGCUG   |
|      | 5064 CACAGCCU CUGAUGA X GAA AGAGAUGA | UCAUCUCUC AGGCUGUG   |
|      | 5076 UCUGAAUU CUGAUGA X GAA AGGCACAG | CUGUGCCUU AAUUCAGA   |
| J. F | 5077 UUCUGAAU CUGAUGA X GAA AAGGCACA | The second of th |
|      | 5080 GUGUUCUG CUGAUGA X GAA AUUAAGGC |  |
|      | 5081 GGUGUUCU CUGAUGA X GAA AAUUAAGG |  |
|      | 5105 CCUCUGCC CUGAUGA X GAA ACGUUCCU |  |
|      | 5116 CCCGUCAG CUGAUGA X GAA AGCCUCUG |  |
| 20   | 5135 GUUCUCAC CUGAUGA X GAA AUUCUUCG |  |
|      | 5156 GAAACCCU CUGAUGA X GAA AGUUUCUG |  |
|      | 5162 CCAGCAGA CUGAUGA X GAA ACCCUGAG |  |
|      | 5163 CCCAGCAG CUGAUGA X GAA AACCCUGA |  |
|      | 5164 ACCCAGCA CUGAUGA X GAA AAACCCUG |  |
| 25   | 5203 AACCCUCA CUGAUGA X GAA ACCUGCCA | UGGCAGGUC UGAGGGUU   |
|      | 5211 UGACAGAG CUGAUGA X GAA ACCCUCAG | CUGAGGGUU CUCUGUCA   |
|      | 5212 UUGACAGA CUGAUGA X GAA AACCCUCA | UGAGGGUUC UCUGUCAA   |
|      | 5214 ACUUGACA CUGAUGA X GAA AGAACCCU |  |
|      | 5218 CGCCACUU CUGAUGA X GAA ACAGAGAA | 122000000  |
| 30   | 5229 UGAGCCUU CUGAUGA X GAA ACCGCCAC | GUGGCGGUA AAGGCUCA   |
|      |                                      |  |

|    |       |          |         |            |     | AGCCUUUA | UAAAGGCUC AGGCUGGU |
|----|-------|----------|---------|------------|-----|----------|--------------------|
|    | 5247  | AGAGGAAG | CUGAUGA | . X        | GAA | ACACCAGC | GCUGGUGUU CUUCCUCU |
|    | 5248  | UAGAGGAA | CUGAUGA | . X        | GAA | AACACCAG | CUGGUGUUC UUCCUCUA |
|    | 5250  | GAUAGAGG | CUGAUGA | . <b>X</b> | GAA | AGAACACC | GGUGUUCUU CCUCUAUC |
| 5  | 5251  | AGAUAGAG | CUGAUGA | X          | GAA | AAGAACAC | GUGUUCUUC CUCUAUCU |
|    | 5254  | UGGAGAUA | CUGAUGA | X          | GAA | AGGAAGAA | UUCUUCCUC UAUCUCCA |
|    | 5256  | AGUGGAGA | CUGAUGA | X          | GAA | AGAGGAAG | CUUCCUCUA UCUCCACU |
|    | 5258  | GGAGUGGA | CUGAUGA | x          | GAA | AUAGAGGA | UCCUCUAUC UCCACUCC |
|    | 5260  | CAGGAGUG | CUGAUGA | X          | GAA | AGAUAGAG | CUCUAUCUC CACUCCUG |
| 10 | 5265  | CCUGACAG | CUGAUGA | X          | GAA | AGUGGAGA | UCUCCACUC CUGUCAGG |
|    | 5270  | GGGGCCU  | CUGAUGA | x          | GAA | ACAGGAGU | ACUCCUGUC AGGCCCCC |
|    | 5283  | AUACUGAG | CUGAUGA | x          | GAA | ACUUGGGG | CCCCAAGUC CUCAGUAU |
|    | 5286  | AAAAUACU | CUGAUGA | x          | GAA | AGGACUUG | CAAGUCCUC AGUAUUUU |
|    | 5290  | AGCUAAAA | CUGAUGA | x          | GAA | ACUGAGGA | UCCUCAGUA UUUUAGCU |
| 15 | 5292  | AAAGCUAA | CUGAUGA | X          | GAA | AUACUGAG | CUCAGUAUU ULAGCUUU |
|    | 5293  | CAAAGCUA | CUGAUGA | x          | GAA | AAUACUGA | UCAGUAUUU UAGCUUUG |
|    | 5294  | ACAAAGCU | CUGAUGA | x          | GAA | AAAUACUG | CAGUAUUUU AGCUUUGU |
|    | 5295  | CACAAAGC | CUGAUGA | x          | GAA | AAAAUACU | AGUAUUUUA GCUUUGUG |
|    | 5299  | AAGCCACA | CUGAUGA | x          | GAA | AGCUAAAA | UUUUAGCUU UGUGGCUU |
| 20 | -5300 | GAAGCCAC | CUGAUGA | X          | GAA | AAGCUAAA | UUUAGCUUU GUGGCUUC |
|    | 5307  | CCAUCAGG | CUGAUGA | X          | GAA | AGCCACAA | UUGUGGCUU CCUGAUGG |
|    | 5308  | GCCAUCAG | CUGAUGA | x          | GAA | AAGCCACA | UGUGGCUUC CUGAUGGC |
|    | 5325  | CCAAUUAA | CUGAUGA | x          | GAA | AUUUUUCU | AGAAAAAUC UUAAUUGG |
|    | 5327  | AACCAAUU | CUGAUGA | x          | GAA | AGAUUUUU | AAAAAUCUU AAUUGGUU |
| 25 | 5328  | CAACCAAU | CUGAUGA | x          | GAA | AAGAUUUU | AAAAUCUUA AUUGGUUG |
|    | 5331  | AACCAACC | CUGAUGA | x          | GAA | AUUAAGAU | AUCUUAAUU GGUUGGUU |
|    | 5335  | AGCAAACC | CUGAUGA | X          | GAA | ACCAAUUA | UAAUUGGUU GGUUUGCU |
|    | 5339  | GGAGAGCA | CUGAUGA | X          | GAA | ACCAACCA | ugguugguu ugcucucc |
|    | 5340  | UGGAGAGC | CUGAUGA | x          | GAA | AACCAACC | GGUUGGUUU GCUCUCCA |
| 30 | 5344  | UAUCUGGA | CUGAUGA | X          | GAA | AGCAAACC | GGUUUGCUC UCCAGAUA |
|    |       |          |         |            |     |          |                    |

|    | 534  | 6 AUUAUCU | G CUGAUG  | A 2        | K GAZ | A AGAGCAAA | UUUGCUCUC CAGAUAAU |
|----|------|-----------|-----------|------------|-------|------------|--------------------|
|    | 535  | 2 CUAGUGA | U CUGAUGA | A )        | ( GA  | A AUCUGGAG | CUCCAGAUA AUCACUAG |
|    | 535  | 5 UGGCUAG | u cugaugi | A 3        | ( GAZ | AUUAUCUG   | CAGAUAAUC ACUAGCCA |
|    | 5359 | AAUCUGG   | C CUGAUGA | <b>A</b> > | GAA   | AGUGAUUA   | UAAUCACUA GCCAGAUU |
| 5  | 536  | 7 AAUUUCG | a cugauga | K A        | GAA   | AUCUGGCU   | AGCCAGAUU UCGAAAUU |
|    | 5368 | UAAUUUC   | G CUGAUGA | X          | GAA   | AAUCUGGC   | GCCAGAUUU CGAAAUUA |
|    | 5369 | GUAAUUU   | CUGAUGA   | X          | GAA   | AAAUCUGG   | CCAGAUUUC GAAAUUAC |
|    | 5375 | UAAAAAGI  | J CUGAUGA | X          | GAA   | AUUUCGAA   | UUCGAAAUU ACUUUUUA |
|    | 5376 | CUAAAAA   | G CUGAUGA | x          | GAA   | AAUUUCGA   | UCGAAAUUA CUUUUUAG |
| 10 | 5379 | CGGCUAA   | CUGAUGA   | x          | GAA   | AGUAAUUU   | AAAUUACUU UUUAGCCG |
|    | 5380 | UCGGCUAA  | CUGAUGA   | X          | GAA   | AAGUAAUU   | AAUUACUUU UUAGCCGA |
|    | 5381 | CUCGGCUA  | CUGAUGA   | x          | GAA   | AAAGUAAU   | AUUACUUUU UAGCCGAG |
|    | 5382 | CCUCGGCU  | CUGAUGA   | x          | GAA   | AAAAGUAA   | UUACUUUUU AGCCGAGG |
|    | 5383 | ACCUCGGC  | CUGAUGA   | X          | GAA   | AAAAAGUA   | UACUUUUUA GCCGAGGU |
| 15 | 5392 | GUUAUCAU  | CUGAUGA   | x          | GAA   | ACCUCGGC   | GCCGAGGUU AUGAUAAC |
|    | 5393 | UGUUAUCA  | CUGAUGA   | x          | GAA   | AACCUCGG   | CCGAGGUUA UGAUAACA |
|    | 5398 | GUAGAUGU  | CUGAUGA   | x          | GAA   | AUCAUAAC   | GUUAUGAUA ACAUCUAC |
|    | 5403 | AUACAGUA  | CUGAUGA   | x          | GAA   | AUGUUAUC   | GAUAACAUC UACUGUAU |
|    | 5405 | GGAUACAG  | CUGAUGA   | X          | GAA   | AGAUGUUA   | UAACAUCUA CUGUAUCC |
| 20 | 5410 | CUAAAGGA  | CUGAUGA   | x          | GAA   | ACAGUAGA   | UCUACUGUA UCCUUUAG |
|    | 5412 | UUCUAAAG  | CUGAUGA   | x          | GAA   | AUACAGUA   | UACUGUAUC CUUUAGAA |
|    | 5415 | AAAUUCUA  | CUGAUGA   | X          | GAA   | AGGAUACA   | UGUAUCCUU UAGAAUUU |
|    | 5416 | AAAAUUCU  | CUGAUGA   | X          | GAA   | AAGGAUAC   | GUAUCCUUU AGAAUUUU |
|    | 5417 | UAAAAUUC  | CUGAUGA   | X          | GAA   | AAAGGAUA   | UAUCCUUUA GAAUUUUA |
| 25 | 5422 | UAGGUUAA  | CUGAUGA   | x          | GAA   | AUUCUAAA   | UUUAGAAUU UUAACCUA |
|    | 5423 | AUAGGUUA  | CUGAUGA   | x          | GAA   | AAUUCUAA   | UUAGAAUUU UAACCUAU |
|    | 5424 | UAUAGGUU  | CUGAUGA   | X          | GAA   | AAAUUCUA   | UAGAAUUUU AACCUAUA |
|    | 5425 | UUAUAGGU  | CUGAUGA   | X          | GAA   | AAAAUUCU   | AGAAUUUUA ACCUAUAA |
|    | 5430 | UAGUUUUA  | CUGAUGA   | x          | GAA   | AGGUUAAA   | UUUAACCUA UAAAACUA |
| 30 | 5432 | CAUAGUUU  | CUGAUGA   | x          | GAA   | AUAGGUUA   | UAACCUAUA AAACUAUG |
|    |      |           |           |            |       |            | _                  |

149

|   | 5438 | AGUAGACA | CUGAUGA | X | GAA | AGUUUUAU | AUAAAACUA | UGUCUACU |
|---|------|----------|---------|---|-----|----------|-----------|----------|
|   | 5442 | AACCAGUA | CUGAUGA | x | GAA | ACAUAGUU | AACUAUGUC | UACUGGUU |
|   | 5444 | GAAACCAG | CUGAUGA | x | GAA | AGACAUAG | CUAUGUCUA | CUGGUUUC |
|   | 5450 | CAGGCAGA | CUGAUGA | X | GAA | ACCAGUAG | CUACUGGUU | UCUGCCUG |
| 5 | 5451 | ACAGGCAG | CUGAUGA | X | GAA | AACCAGUA | UACUGGUUU | CUGCCUGU |
|   | 5452 | CACAGGCA | CUGAUGA | X | GAA | AAACCAGU | ACUGGUUUC | UGCCUGUG |

Where "X" represents stem II region of a HH ribozyme (Hertel et al., 1992 Nucleic Acids Res. 20 3252). The length of stem II may be  $\geq$  2 base-pairs.

Table VII: Mouse flk-1 VEGF Receptor-Hairpin Ribozyme and Substrate Sequences

| Substrate            | GGGCCCA GAC UGUGUA  | UCCCGCA GCC GGGAUAAC                                      | CCUGGCU GAC CCGAUUCC                                      | CUGACCC GAU UCCGCGGA                                      | GGACACC GCU GACAGCCG                                      | GCUGACA GCC GFGGFT1GG                                     | AGCCGCG GCU GGAGCCAG                                      | CUCCCC GUC MIRCECIN                                       | CCAUACC GCC 11Clights                                     | GCUAGCU GIIC GCIICUGIIG                                   | CCGAGCC GCC 11C11G11GG                                    | CCCUICA GAIT HACHINGS                                     | CUCCACIT GIIIT HAIGHCHA                                  | GALILIACIA GALL CACCALILLO                                | AUCCCCU GCC GAGGGUCG                                     |
|----------------------|---|---|---|---|---|---|---|---|---|---|---|---|--|---|--|
| HP Ribozyme Sequence | GGGACACA AGAA GGGCCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GUUAUCCC AGAA GCGGGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGAAUCGG AGAA GCCAGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UCCGCGGA AGAA GGUCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CGGCUGUC AGAA GUGUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CCAGCCGC AGAA GUCAGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CUGGCUCC AGAA GCGGCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CAGCGCAA AGAA GGGGAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GUCACAGA AGAA GUAUGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CACAGAGC AGAA GCUAGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CCCACAGA AGAA GCUCGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UGCAAGUA AGAA GAAGGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UAGACAUA AGAA GUGGAG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA | GAAUGGUG AGAA GUAAUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CGACCCUC AGAA GGGGAU ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA |
|                      | ೨೨೨೨೨ ۱   | GCGGGA  | GCCAGG  | GGUCAG  | GUGUCC  | GUCAGC  | CCGCCU  | GGGGAG  | GUAUGG  | GCUAGC  | Bonce   | GAAGGG  | GUGGAG   | GUAAUC  | GGGGAU   |
|                      | AGA   | AGA   | AGAA  | AGAA   | AGAA  | AGAA   |
| 1 .                  | GGGACACA  | GUUAUCCC  | GGAAUCGG  | UCCGCGGA  | ວດອດວດອວ  | CCAGCCGC  | cuggcucc  | CAGCGCAA  | GUCACAGA  | CACAGAGC  | CCCACAGA  | UGCAAGUA  | UAGACAUA   | GAAUGGUG  | CGACCCUC   |
| nt.<br>Posi-<br>tion | 74  | 88  | 105   | 110   | 125   | 132   | 138   | 175   | 199   | 309   | 342   | 434   | 630  | 655   | 739  |
|                      | ம   |   |   |   |   | 10  |   |   |   |   | 15  |   |  |   |  |

CGUUAAGC

GAC

UCCUACG

GCUUAACG AGAA GUAGGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA

2639

ACCUGEU GEC CAGECAAC JGUUCCG GAU GGAAACAG CCUAUCA GUC UAUCAUGU GGAGAAAA GUGGACG GAU GAUCAAGA UVACCCA GCU CCUGAUAU CGGUGAGA AUGCACA GUC UACGCCAA GAAGCCU GCU CCUACAGA AUGCCCU GAU UGAAGGAA GCCCAGCC UGUCCCU GUU GUGCACUG AACAUCG GUC CACAUGGG CACACCA GUU UGCAAGAA GCU CAAGAUAA GCU CAUCAUCC BGAACCU GAC UAUCCGCA UCCUACA GAC CCGGCCAA GCUAUCU GCC CACCCCA GAU GCAACCU GCU UCAAACA UUGCUCU CUGUTUÓC AGAA GGAACA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GAUAGG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA AUAUCAGG AGAA GGGUAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCUCACCG AGAA GGGGUG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGCUUC ACCAGAGAACACGCUUGUGGUACAUUACCUGGUA GUAGGA ACCAGAGAACACGUUGUGGUACAUUACCUGGUA UUCCUUCA AGAA GGGCAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA SGCUGGGC AGAA GGUUGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GCAGGU ACCAGAGAAACACGCUGGUGGGAACAUUACCUGGUA CAGUGCAC AGAA GGGACA ACCAGAAAACACACGUUGUGGUACAUUACCUGGUA CCCAUGUG AGAA GAUGUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAUAGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GUCCAC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GUGCAU ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GGUGUG ACCAGAGAAACACGCUUGUGGGAACAUUACCUGGUA JUAUCUUG AGAA GAGCAA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA SGAUGAUG AGAA GUUUGA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA UGCGGAUA AGAA GGUUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGAA AGAA UUGGCGUA AGAA UCUGUAGG AGAA UUCUUGCA AGAA ACAUGAUA AGAA JUJUCUCC AGAA GUUGGCUG AGAA JCUUGAUC nnaaccaa 1365 1985 1002 1229 1556 1629 1687 1696 1796 1950 1953 2055 2082 2208 2252 2444 920 807 ហ 10 15

UGCUGCA GUU CACGCUGA

UCAGCGUG AGAA GCAGCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA

4278

GGAUCCA GAU GAAUUGCC GGGACCG GCU GAAACUAG UGAGGCA GAC GCUUUUGG CAGGCUUU ACUUCCU GAC CUUGGAGC UGUUACA GCU UCCAAGUG AGACCCG GAU UAUGUCAG GAUGCCC GAC UCCCUUUG GACUUCG GCU UGGCCCGG GGCUCCU GAC UACACUAC CUGGACU GCU GGCAUGAG UGUACCA GAC CAUGCUGG UCUCCCU GCC UACCUCAC CUCACCU GUU UCCUGUAU GAUCCCA GAU GACAGCCA CCAACCA GAC CAGUGGCU GCUACCA GUC UGGGUAUC UCACUCA GAU GACACAGA GCU UCUGCCA GGCAAUUC AGAA GGAUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGUCCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GCCUCA ACCAGAGAACACGUUGUGGUACAUUACCUGGUA AAAGCCUG AGAA GGCAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCUCCAAG AGAA GGAAGU ACCAGAGAAACACGCUGGUGGUACAUUACCUGGUA CACUUGGA AGAA GUAACA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCGGGCCA AGAA GAAGUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUGACAUA AGAA GGGUCU ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CAAAGGGA AGAA GGCAUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GUAGUGUA AGAA GGAGCC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CCAGCAUG AGAA GGUACA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUCAUGCC AGAA GUCCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GUGAGGUA AGAA GGGAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGCCACUG AGAA GGUUGG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA AUACAGGA AGAA GGUGAG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA UGGCUGUC AGAA GGGAUC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGUAGC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA UCUGUGUC AGAA GAGUGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CUAGUUUC AGAA CCAAAAGC AGAA GAUACCCA AGAA 2777 2832 3199 3278 3304 3421 3450 3475 3663 3689 3860 3703 3873 4038 4196 4212 4181 S 10 15

UCACGCU GAC UCAGGGAC

153 naguacon ena acadecua CACUGCA GCU CACCUCCU nenccce ecn ccecccc GAC UGCAAGGA CGAGUCU GUC UACCUUGG GAGAGCG GUU GGAGCCUG GCCUGCA GAU GCAUUGUG GUU UAAAUGGA CCCAACUC AGGUGCU GCU UAGAUUUU suscen seu sussueue GGACUCU GUC CUCCAAGA GGCAGGGU CUUCACA GUC GGGUUACA UCUNACGO GCU UGCUCCUU GGUUUCU GCU GGGUGGAG BGCUCCU GAC GGGGCCGA ggg GAC gcc CGGCUCC ACCUCCU GACCUCA AAAGGCG UGAUGCA CCUUCCG UCCAUTUA AGAA GGAGGU ACCAGAGAAACACACGUUGUGGUACAUTACCUGGUA GGACCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGGGGCGG AGAA GGGACA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAGUUGGG AGAA GAGCCG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA UCCUUGCA AGAA GAGGUC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA GCAGUG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA AAAAUCUA AGAA GCACCU ACCAGAGAAACACGCUUGUGGUACAUUACCUGGUA GAGACCAC AGAA GGGCAC ACCAGAGAACACACG JGUGGUACAUUACCUGGUA AGAA GAGUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCAAGGUA AGAA GACUCG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CAGGCUCC AGAA GCUCUC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA CACAAUGC AGAA GCAGGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA ACCCUGCC AGAA GCCUUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UGUAACCC AGAA GUGAAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA ACGUAAGA AGAA GGAAGG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA AAGGAGCA AGAA GCAUCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA JCGGCCCC AGAA GGAGCC ACCAGAGAACACACGUJGUGGGJACAUUACCUGGJA CUCCACCC AGAA GAAACC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGAA GGAGCCGG AGAA UCUUGGAG AGGAGGUG 4349 4307 4318 4338 4344 4383 4626 4836 4462 4574 4723 4823 4896 4938 4996 5118 5165 5042

10

15

GUCCCUGA AGAA GCGUGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA

4287

വ

| GCUUCCU GAU GGCAGAAA                                      | CUAGCCA GAU UUCGAAAU                                      | Gennaca ecc aeacaeca                                |
|---|---|---|
| UUUCUGCC AGAA GGAAGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AUUUCGAA AGAA GGCUAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CACA AGAA GAAACC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA |
| GGAAGC  | GGCUAG  | GAAACC  |
| AGAA  | AGAA  | AGAA  |
| ນນາດນອດດ  | AUUUCGAA  | AGCACACA  |
| 5310  | 5363  | 5453  |

155

## Table VIII: Mouse flt-1 VEGF Receptor-Hammerhead Ribozyme and Substrate Sequence

|    | nt.   | 1        | HH Riboz | λш         | e Se | quence   | Substrate          |
|----|-------|----------|----------|------------|------|----------|--------------------|
|    | Posi- |          |          |            |      | •        |                    |
| 5  | tion  |          |          |            |      |          |                    |
|    | 17    | GUGAGCAA | CUGAUGA  | . <b>X</b> | GAA  | ACGCGGCC | GGCCGCGUC UUGCUCAC |
|    | 19    | UGGUGAGC | CUGAUGA  | X          | GAA  | AGACGCGG | CCGCGUCUU GCUCACCA |
|    | 23    | ACCAUGGU | CUGAUGA  | X          | GAA  | AGCAAGAC | GUCUUGCUC ACCAUGGU |
|    | 32    | CAGCAGCU | CUGAUGA  | x          | GAA  | ACCAUGGU | ACCAUGGUC AGCUGCUG |
| 10 | 53    | UAAGGCAA | CUGAUGA  | x          | GAA  | ACCGCGGU | ACCGCGGUC UUGCCUUA |
|    | 55    | CGUAAGGC | CUGAUGA  | X          | GAA  | AGACCGCG | CGCGGUCUU GCCUUACG |
|    | 60    | CAGCGCGU | CUGAUGA  | X          | GAA  | AGGCAAGA | UCUUGCCUU ACGCGCUG |
|    | 61    | GCAGCGCG | CUGAUGA  | x          | GAA  | AAGGCAAG | CUUGCCUUA CGCGCUGC |
|    | 71    | AGACACCC | CUGAUGA  | x          | GAA  | AGCAGCGC | GCGCUGCUC GGGUGUCU |
| 15 | 78    | GAGAAGCA | CUGAUGA  | x          | GAA  | ACACCCGA | ucggguguc ugcuucuc |
|    | 83    | CCUGUGAG | CUGAUGA  | x          | GAA  | AGCAGACA | UGUCUGCUU CUCACAGG |
|    | 84    | UCCUGUGA | CUGAUGA  | x          | GAA  | AAGCAGAC | GUCUGCUUC UCACAGGA |
|    | 86    | UAUCCUGU | CUGAUGA  | X          | GAA  | AGAAGCAG | CUGCUUCUC ACAGGAUA |
|    | 94    | CUGAGCCA | CUGAUGA  | x          | GAA  | AUCCUGUG | CACAGGAUA UGGCUCAG |
| 20 | 100   | UCGACCCU | CUGAUGA  | x          | GAA  | AGCCAUAU | AUAUGGCUC AGGGUCGA |
|    | 106   | UUAACUUC | CUGAUGA  | x          | GAA  | ACCCUGAG | CUCAGGGUC GAAGUUAA |
|    | 112   | GCACUUUU | CUGAUGA  | x          | GAA  | ACUUCGAC | GUCGAAGUU AAAAGUGC |
|    | 113   | GGCACUUU | CUGAUGA  | x          | GAA  | AACUUCGA | UCGAAGUUA AAAGUGCC |
|    | 132   | GCCUUUUA | CUGAUGA  | x          | GAA  | ACUCAGUU | AACUGAGUU UAAAAGGC |
| 25 | 133   | UGCCUUUU | CUGAUGA  | x          | GAA  | AACUCAGU | ACUGAGUUU AAAAGGCA |
|    | 134   | GUGCCUUU | CUGAUGA  | x          | GAA  | AAACUCAG | CUGAGUUUA AAAGGCAC |
|    | 152   | GCUUGCAU | CUGAUGA  | x          | GAA  | ACAUGCUG | CAGCAUGUC AUGCAAGC |
|    | 171   | GAGAAAGA | CUGAUGA  | x          | GAA  | AGUCUGGC | GCCAGACUC UCUUUCUC |
|    | 173   | UUGAGAAA | CUGAUGA  | x          | GAA  | AGAGUCUG | CAGACUCUC UUUCUCAA |
| 30 | 175   | ACUUGAGA | CUGAUGA  | x          | GAA  | AGAGAGUC | GACUCUCUU UCUCAAGU |
|    | 176   | CACUUGAG | CUGAUGA  | x          | GAA  | AAGAGAGU | ACUCUCUUU CUCAAGUG |
|    | 177   | GCACUUGA | CUGAUGA  | x          | GAA  | AAAGAGAG | CUCUCUUUC UCAAGUGC |

|    | 179         | CUGCACUU CUGAUGA X GAA AGAAAGAG | CHICHTHICH ANGUAGO   |
|----|-------------|---------------------------------|--|
|    | 205         | GAGACCAU CUGAUGA X GAA AGUGGGCU | STOREST MAGOGLAG   |
|    | 211         | UGGGCAGA CUGAUGA X GAA ACCAUGAG | AGCCCACUC AUGGUCUC   |
|    | 213         | CGUGGGCA CUGAUGA X GAA AGACCAUG | THE STOCK OCOGCICA   |
| 5  | 254         | GGGGGAGU CUGAUGA X GAA AUGCUCAG | THE PERSON OF COMME  |
|    | 258         | CGAUGGGG CUGAUGA X GAA AGUGAUGC | CUGAGCAUC ACUCCCCC   |
|    | 265         | CACAGGCC CUGAUGA X GAA AUGGGGGA | GCAUCACUC CCCCAUCG   |
|    | 282         | UUGCCUGU CUGAUGA X GAA AUCCCUCC | UCCCCCAUC GGCCUGUG   |
|    | 292         | UGCUGCAG CUGAUGA X GAA AUUGCCUG | THE PERSON NEADGENA  |
| 10 | <b>29</b> 3 | GUGCUGCA CUGAUGA X GAA AAUUGCCU | CAGGCAAUU CUGCAGCA   |
|    | 304         | CCAAGGUC CUGAUGA X GAA AGGUGCUG | AGGCAAUUC UGCAGCAC   |
|    | 310         | CCGUGUCC CUGAUGA X GAA AGGUCAAG | CAGCACCUU GACCUUGG   |
|    | 341         | CAGGUGUA CUGAUGA X GAA AGGCCCGU | out the same of th |
|    | 343         | UACAGGUG CUGAUGA X GAA AGAGGCCC | ACGGGCCUC UACACCUG   |
| 15 | 351         |                                 | GGGCCUCUA CACCUGUA   |
|    | 355         | GAGGUAUC CUGAUGA X GAA ACAGGUGU | ACACCUGUA GAUACCUC   |
|    | 359         | UAGGGAGG CUGAUGA X GAA AUCUACAG | CUGUAGAUA CCUCCCUA   |
|    | 363         | GAUGUAGG CUGAUGA X GAA AGGUAUCU | AGAUACCUC CCUACAUC   |
|    | 367         | AGUAGAUG CUGAUGA X GAA AGGGAGGU | ACCUCCCUA CAUCUACU   |
| 20 |             | UCGAAGUA CUGAUGA X GAA AUGUAGGG | CCCUACAUC UACUUCGA   |
| 20 | 369         | CUUCGAAG CUGAUGA X GAA AGAUGUAG | CUACAUCUA CUUCGAAG   |
|    | 372         | UUUCUUCG CUGAUGA X GAA AGUAGAUG | CAUCUACUU CGAAGAAA   |
|    | 373         | UUUUCUUC CUGAUGA X GAA AAGUAGAU | AUCUACUUC GAAGAAAA   |
|    | 394         | AGAUUGAA CUGAUGA X GAA AUUCCGCU | AGCGGAAUC UUCAAUCU   |
|    | 396         | GUAGAUUG CUGAUGA X GAA AGAUUCCG | CGGAAUCUU CAAUCUAC   |
| 25 | 397         | UGUAGAUU CUGAUGA X GAA AAGAUUCC | GGAAUCUUC AAUCUACA   |
|    | 401         | AAUAUGUA CUGAUGA X GAA AUUGAAGA | UCUUCAAUC UACAUAUU   |
|    | 403         | CAAAUAUG CUGAUGA X GAA AGAUUGAA | UUCAAUCUA CAUAUUUG   |
|    | 407         | CUAACAAA CUGAUGA X GAA AUGUAGAU | AUCUACAUA UUUGUUAG   |
|    | 409         | CACUAACA CUGAUGA X GAA AUAUGUAG | CUACAUAUU UGUUAGUG   |
| 30 | 410         | UCACUAAC CUGAUGA X GAA AAUAUGUA | UACAUAUUU GUUAGUGA   |
|    | 413         | GCAUCACU CUGAUGA X GAA ACAAAUAU | AUAUUUGUU AGUGAUGC   |
|    | 414         | UGCAUCAC CUGAUGA X GAA AACAAAUA | UAUUUGUUA GUGAUGCA   |
|    | 429         | UAUGAAAG CUGAUGA X GAA ACUCCCUG | CAGGGAGUC CUUUCAUA   |
|    |             |                                 |  |

|            | 432         | CUCUAUGA | CUGAUGA | X          | GAA | AGGACUCC | GGAGUCCUU | UCAUAGAG |
|------------|-------------|----------|---------|------------|-----|----------|-----------|----------|
|            | 433         | UCUCUAUG | CUGAUGA | X          | GAA | AAGGACUC | GAGUCCUUU | CAUAGAGA |
|            | 434         | AUCUCUAU | CUGAUGA | x          | GAA | AAAGGACU | AGUCCUUUC | AUAGAGAU |
|            | 437         | UGCAUCUC | CUGAUGA | x          | GAA | AUGAAAGG | CCUUUCAUA | GAGAUGCA |
| 5          | 455         | AGUUUGGG | CUGAUGA | X          | GAA | AUGUCAGU | ACUGACAUA | CCCAAACU |
|            | 464         | AUGUGCAC | CUGAUGA | X          | GAA | AGUUUGGG | CCCAAACUU | GUGCACAU |
|            | 491         | GGGAUGAU | CUGAUGA | X          | GAA | AGCUGUCU | AGACAGCUC | AUCAUCCC |
|            | 494         | CAGGGGAU | CUGAUGA | X          | GAA | AUGAGCUG | CAGCUCAUC | AUCCCCUG |
|            | 497         | CGGCAGGG | CUGAUGA | X          | GAA | AUGAUGAG | CUCAUCAUC | CCCUGCCG |
| 10         | 514         | CGUUGGGU | CUGAUGA | X          | GAA | ACGUCACC | GGUGACGUC | ACCCAACG |
|            | 524         | GUGACUGU | CUGAUGA | X          | GAA | ACGUUGGG | CCCAACGUC | ACAGUCAC |
|            | 530         | UUUAGGGU | CUGAUGA | X          | GAA | ACUGUGAC | GUCACAGUC | ACCCUAAA |
|            | 536         | AACUUUUU | CUGAUGA | X          | GAA | AGGGUGAC | GUCACCCUA | AAAAAGUU |
|            | 544         | CAAAUGGA | CUGAUGA | x          | GAA | ACUUUUUU | AAAAAAGUU | UCCAUUUG |
| 15         | <b>54</b> 5 | UCAAAUGG | CUGAUGA | x          | GAA | AACUUUUU | AAAAAGUUU | CCAUUUGA |
|            | 546         | AUCAAAUG | CUGAUGA | X          | GAA | AAACUUUU | AAAAGUUUC | CAUUUGAU |
|            | 550         | GAGUAUCA | CUGAUGA | x          | GAA | AUGGAAAC | GUUUCCAUU | UGAUACUC |
|            | 551         | AGAGUAUC | CUGAUGA | x          | GAA | AAUGGAAA | UUUCCAUUU | GAUACUCU |
|            | 555         | GGUAAGAG | CUGAUGA | x          | GAA | AUCAAAUG | CAUUUGAUA | CUCUUACC |
| 20         | 558         | AGGGGUAA | CUGAUGA | x          | GAA | AGUAUCAA | UUGAUACUC | UUACCCCU |
|            | 560         | UCAGGGGU | CUGAUGA | X          | GAA | AGAGUAUC | GAUACUCUU | ACCCCUGA |
|            | 561         | AUCAGGGG | CUGAUGA | x          | GAA | AAGAGUAU | AUACUCUUA | CCCCUGAU |
|            | 581         | UCCCAUGU | CUGAUGA | X          | GAA | AUUCUUUG | CAAAGAAUA | ACAUGGGA |
|            | 594         | GCCUCUCC | CUGAUGA | X          | GAA | ACUGUCCC | GGGACAGUA | GGAGAGGC |
| <b>2</b> 5 | 604         | CUAUUAUA | CUGAUGA | X          | GAA | AGCCUCUC | GAGAGGCUU | UAUAAUAG |
|            | 605         | GCUAUUAU | CUGAUGA | X          | GAA | AAGCCUCU | AGAGGCUUU | AUAAUAGC |
|            | 606         | UGCUAUUA | CUGAUGA | X          | GAA | AAAGCCUC | GAGGCUUUA | UAAUAGCA |
|            | 608         | UUUGCUAU | CUGAUGA | <b>X</b> , | GAA | AUAAAGCC | GGCUUUAUA | AUAGCAAA |
|            | 611         | GCAUUUGC | CUGAUGA | x          | GAA | AUUAUAAA | UUUAUAAUA | GCAAAUGC |
| 30         | 625         | UCUCUUUG | CUGAUGA | x          | GAA | ACGUUGCA | UGCAACGUA | CAAAGAGA |
|            | 635         | AGCAGUCC | CUGAUGA | X          | GAA | AUCUCUUU | AAAGAGAUA | GGACUGCU |
|            | 662         | UGCCCGUU | CUGAUGA | X          | GAA | ACGGUGGC | GCCACCGUC | AACGGGCA |
|            | 676         | UUGUCUGG | CUGAUGA | X          | GAA | ACAGGUGC | GCACCUGUA | CCAGACAA |
|            |             |          |         |            |     |          |           |          |

|     | 688        | GGGUCAGA CUGAUGA X GAA AGUUUGUC | GACAAACUA UCUGACCC                      |
|-----|------------|---------------------------------|---|
|     | 690        | AUGGGUCA CUGAUGA X GAA AUAGUUUG |   |
|     | 699        | GGUCUGCC CUGAUGA X GAA AUGGGUCA |   |
|     | 711        | UAGGAUUG CUGAUGA X GAA AUUGGUCU |   |
| 5   | 716        | ACAUCUAG CUGAUGA K GAA AUUGUAUU | AAUACAAUC CUAGAUGU                      |
|     | 719        | UGGACAUC CUGAUGA X GAA AGGAUUGU | ACAAUCCUA GAUGUCCA                      |
|     | 725        | CGUAUUUG CUGAUGA X GAA ACAUCUAG | CUAGAUGUC CAAAUACG                      |
|     | 731        | GGCGGGCG CUGAUGA X GAA AUUUGGAC | GUCCAAAUA CGCCCGCC                      |
|     | 758        | UGCCCGUG CUGAUGA X GAA AGCAGUCU | AGACUGCUC CACGGGCA                      |
| 10  | 771        | GAGGACAA CUGAUGA X GAA AGUCUGCC | GGCAGACUC UUGUCCUC                      |
|     | 773        | UUGAGGAC CUGAUGA X GAA AGAGUCUG | CAGACUCUU GUCCUCAA                      |
|     | 776        | CAGUUGAG CUGAUGA X GAA ACAAGAGU | ACUCUUGUC CUCAACUG                      |
|     | 779        | GUGCAGUU CUGAUGA X GAA AGGACAAG | CUUGUCCUC AACUGCAC                      |
|     | 803        | CUCGUAUU CUGAUGA X GAA AGCUCCGU | ACGGAGCUC AAUACGAG                      |
| 15  | 807        | CACCCUCG CUGAUGA X GAA AUUGAGCU | AGCUCAAUA CGAGGGUG                      |
|     | 831        | ACCAGGGU CUGAUGA X GAA AUUCCAGC | GCUGGAAUU ACCCUGGU                      |
| •   | 832        | UACCAGGG CUGAUGA X GAA AAUUCCAG | CUGGAAUUA CCCUGGUA                      |
|     | 840        | AGUUGCUU CUGAUGA X GAA ACCAGGGU |   |
| 20  | 849        | UGCUCUCU CUGAUGA X GAA AGUUGCUU | AAGCAACUA AGAGAGCA                      |
| 20  | 859        | GCCUUAUA CUGAUGA X GAA AUGCUCUC | GAGAGCAUC UAUAAGGC                      |
|     | 861<br>863 | CUGCCUUA CUGAUGA X GAA AGAUGCUC | GAGCAUCUA UAAGGCAG                      |
|     | 875        | CGCUGCCU CUGAUGA X GAA AUAGAUGC | GCAUCUAUA AGGCAGCG                      |
|     | 888        | CUCCGGUC CUGAUGA X GAA AUCCGCUG | CAGCGGAUU GACCGGAG                      |
| 25  | 889        | GUUGUGGG CUGAUGA X GAA AUGGCUCC | GGAGCCAUU CCCACAAC                      |
|     | 904        | UGUUGUGG CUGAUGA X GAA AAUGGCUC | - Carcing                               |
|     | 905        | CACUGUGG CUGAUGA X GAA ACACAUUG |   |
|     | 914        | ACACUGUG CUGAUGA X GAA AACACAUU | a = = = = = = = = = = = = = = = = = = = |
|     | 915        | AUCUUAAG CUGAUGA X GAA ACACUGUG | CACAGUGUU CUUAAGAU                      |
| 30  | 917        | GAUCUUAA CUGAUGA X GAA AACACUGU | ACAGUGUUC UUAAGAUC                      |
| - • | 918        | UUGAUCUU CUGAUGA X GAA AGAACACU | AGUGUUCUU AAGAUCAA                      |
|     | 923        | GUUGAUCU CUGAUGA X GAA AAGAACAC | GUGUUCUUA AGAUCAAC                      |
|     | 953        | ACAUUGUU CUGAUGA X GAA AUCUUAAG | CUUAAGAUC AACAAUGU                      |
|     | 333        | CAGGUGUA CUGAUGA X GAA AGCCCCUU | AAGGGGCUC UACACCUG                      |

PCT/US96/17480 WO 97/15662

|    | 955  | GACAGGUG | CUGAUGA | X | GAA | AGAGCCCC | GGGGCUCUA | CACCUGUC |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 963  | CUUCACGC | CUGAUGA | x | GAA | ACAGGUGU | ACACCUGUC | GCGUGAAG |
|    | 979  | GGAACGAG | CUGAUGA | x | GAA | ACCCACUC | GAGUGGGUC | CUCGUUCC |
|    | 982  | ACUGGAAC | CUGAUGA | x | GAA | AGGACCCA | ugguccuc  | GUUCCAGU |
| 5  | 985  | AAGACUGG | CUGAUGA | x | GAA | ACGAGGAC | guccucguu | CCAGUCUU |
|    | 986  | AAAGACUG | CUGAUGA | x | GAA | AACGAGGA | uccucguuc | CAGUCUUU |
|    | 991  | UGUUGAAA | CUGAUGA | x | GAA | ACUGGAAC | GUUCCAGUC | UUUCAACA |
|    | 993  | GGUGUUGA | CUGAUGA | x | GAA | AGACUGGA | UCCAGUCUU | UCAACACC |
|    | 994  | AGGUGUUG | CUGAUGA | x | GAA | AAGACUGG | CCAGUCUUU | CAACACCU |
| 10 | 995  | GAGGUGUU | CUGAUGA | x | GAA | AAAGACUG | CAGUCUUUC | AACACCUC |
|    | 1003 | CAUGCACG | CUGAUGA | x | GAA | AGGUGUUG | CAACACCUC | CGUGCAUG |
|    | 1015 | CUUUUUCA | CUGAUGA | x | GAA | ACACAUGC | GCAUGUGUA | UGAAAAAG |
|    | 1027 | CACUGAUG | CUGAUGA | x | GAA | AUCCUUUU | AAAAGGAUU | CAUCAGUG |
|    | 1028 | ACACUGAU | CUGAUGA | x | GAA | AAUCCUUU | AAAGGAUUC | AUCAGUGU |
| 15 | 1031 | UUCACACU | CUGAUGA | x | GAA | AUGAAUCC | GGAUUCAUC | AGUGUGAA |
|    | 1044 | CUGCUUCC | CUGAUGA | X | GAA | AUGUUUCA | UGAAACAUC | GGAAGCAG |
|    | 1084 | GCCGAUAG | CUGAUGA | x | GAA | ACCGUCUU | AAGACGGUC | CUAUCGGC |
|    | 1087 | ACAGCCGA | CUGAUGA | x | GAA | AGGACCGU | ACGGUCCUA | UCGGCUGU |
|    | 1089 | GGACAGCC | CUGAUGA | x | GAA | AUAGGACC | GGUCCUAUC | GCCUGUCC |
| 20 | 1096 | CUUUCAUG | CUGAUGA | x | GAA | ACAGCCGA | UCGGCUGUC | CAUGAAAG |
|    | 1114 | GGGAGGGG | CUGAUGA | x | GAA | AGGCCUUC | GAAGGCCUU | ccccuccc |
|    | 1115 | GGGGAGGG | CUGAUGA | x | GAA | AAGGCCUU | AAGGCCUUC | cccucccc |
|    | 1120 | UUUCUGGG | CUGAUGA | x | GAA | AGGGGAAG | cunccccnc | CCCAGAAA |
|    | 1130 | AACCAUAC | CUGAUGA | x | GAA | AUUUCUGG | CCAGAAAUC | GUAUGGUU |
| 25 | 1133 | UUUAACCA | CUGAUGA | x | GAA | ACGAUUUC | GAAAUCGUA | UGGUUAAA |
|    | 1138 | CAUCUUUU | CUGAUGA | x | GAA | ACCAUACG | CGUAUGGUU | AAAAGAUG |
|    | 1139 | CCAUCUUU | CUGAUGA | x | GAA | AACCAUAC | GUAUGGUUA | AAAGAUGG |
|    | 1150 | UUGCAGGC | CUGAUGA | X | GAA | AGCCAUCU | AGAUGGCUC | GCCUGCAA |
|    | 1162 | CAGACUUC | CUGAUGA | x | GAA | AUGUUGCA | UGCAACAUU | GAAGUCUG |
| 30 | 1168 | AGCGAGCA | CUGAUGA | x | GAA | ACUUCAAU | AUUGAAGUC | UGCUCGCU |
|    | 1173 | CAAAUAGC | CUGAUGA | X | GAA | AGCAGACU | AGUCUGCUC | GCUAUUUG |
|    | 1177 | GUACCAAA | CUGAUGA | X | GAA | AGCGAGCA | UGCUCGCUA | UUUGGUAC |
|    | 1179 | AUGUACCA | CUGAUGA | X | GAA | AUAGCGAG | CUCGCUAUU | UGGUACAU |
|    |      |          |         |   |     |          |           |          |

|     | 1180 | CAUGUACC CUGAUGA X GAA AAUAGCGA | UCGCUAUUU GGUACAUG   |
|-----|------|---------------------------------|--|
|     | 1184 | UAGCCAUG CUGAUGA X GAA ACCAAAUA | UAUUUGGUA CAUGGCUA   |
|     | 1192 | UUAAUGAG CUGAUGA X GAA AGCCAUGU | ACAUGGCUA CUCAUUAA   |
|     | 1195 | UAAUUAAU CUGAUGA X GAA AGUAGCCA | UGGCUACUC AUUAAUUA   |
| 5   | 1198 | UGAUAAUU CUGAUGA X GAA AUGAGUAG | CUACUCAUU AAUUAUCA   |
|     | 1199 | UUGAUAAU CUGAUGA X GAA AAUGAGUA | UACUCAUUA AUUAUCAA   |
|     | 1202 | UCUUUGAU CUGAUGA X GAA AUUAAUGA | UCAUUAAUU AUCAAAGA   |
|     | 1203 | AUCUUUGA CUGAUGA X GAA AAUUAAUG | CAUUAAUUA UCAAAGAU   |
|     | 1205 | ACAUCUUU CUGAUGA X GAA AUAAUUAA |  |
| 10  | 1237 | AGAUCGUA CUGAUGA X GAA AGUCCCCU |  |
|     | 1239 | CAAGAUCG CUGAUGA X GAA AUAGUCCC | GGGACUAUA CGAUCUUG   |
|     | 1244 | CCCAGCAA CUGAUGA X GAA AUCGUAUA |  |
|     | 1246 | UGCCCAGC CUGAUGA X GAA AGAUCGUA | UACGAUCUU GCUGGGCA   |
|     | 1256 | GACUGCUU CUGAUGA X GAA AUGCCCAG | CUGGGCAUA AAGCAGUC   |
| 15  | 1264 | AUAGCCUU CUGAUGA X GAA ACUGCUUU |  |
|     | 1271 | UUUUUAAA CUGAUGA X GAA AGCCUUGA | UCAAGGCUA UUUAAAAA   |
|     | 1273 | GGUUUUUA CUGAUGA X GAA AUAGCCUU | AAGGCUAUU UAAAAACC   |
|     | 1274 | AGGUUUUU CUGAUGA X GAA AAUAGCCU | - ISSUECCO   |
| 2.2 | 1275 | GAGGUUUU CUGAUGA X GAA AAAUAGCC | GGCUAUUUA AAAACCUC   |
| 20  | 1283 | GUGGCAGU CUGAUGA X GAA AGGUUUUU | AAAAACCUC ACUGCCAC   |
|     | 1293 | UACAAUGA CUGAUGA X GAA AGUGGCAG | CUGCCACUC UCAUUGUA   |
|     | 1295 | UUUACAAU CUGAUGA X GAA AGAGUGGC | GCCACUCUC AUUGUAAA   |
|     | 1298 | ACGUUUAC CUGAUGA X GAA AUGAGAGU | ACUCUCAUU GUAAACGU   |
| 25  | 1301 | UUCACGUU CUGAUGA X GAA ACAAUGAG | CUCAUUGUA AACGUGAA   |
| 25  | 1314 | GUAGAUCU CUGAUGA X GAA AGGUUUCA | The state of the s |
|     | 1319 | UUUUCGUA CUGAUGA X GAA AUCUGAGG |  |
|     | 1321 | ACUUUUCG CUGAUGA X GAA AGAUCUGA | UCAGAUCUA CGAAAAGU   |
|     |      | AGGACACG CUGAUGA X GAA ACUUUUCG | CGAAAAGUC CGUGUCCU   |
| 30  | 1336 | GAAGCGAG CUGAUGA X GAA ACACGGAC | GUCCGUGUC CUCGCUUC   |
| 30  | 1339 | UUGGAAGC CUGAUGA X GAA AGGACACG | CGUGUCCUC GCUUCCAA   |
|     | 1343 | GGGCUUGG CUGAUGA X GAA AGCGAGGA | UCCUCGCUU CCAAGCCC   |
|     | 1344 | UGGGCUUG CUGAUGA X GAA AAGCGAGG | CCUCGCUUC CAAGCCCA   |
|     | 1356 | CGGAUAGA CUGAUGA X GAA AGGUGGGC | GCCCACCUC UCUAUCCG   |

|    | 1358 | AGCGGAUA CUGA  | JGA X | GAA | AGAGGUGG | CCACCUCUĆ UAUCCGCU |
|----|------|----------------|-------|-----|----------|--------------------|
|    | 1360 | CCAGCGGA CUGA  | JGA X | GAA | AGAGAGGU | ACCUCUCUA UCCGCUGG |
|    | 1362 | GCCCAGCG CUGA  | JGA X | GAA | AUAGAGAG | CUCUCUAUC CGCUGGGC |
|    | 1382 | CAAGUGAG CUGA  | JGA X | GAA | ACUUGUCU | AGACAAGUC CUCACUUG |
| 5  | 1385 | GUGCAAGU CUGA  | JGA X | GAA | AGGACUUG | CAAGUCCUC ACUUGCAC |
|    | 1389 | CACGGUGC CUGAL | JGA X | GAA | AGUGAGGA | UCCUCACUU GCACCGUG |
|    | 1399 | GGAUGCCA CUGAU | JGA X | GAA | ACACGGUG | CACCGUGUA UGGCAUCC |
|    | 1406 | GGCCGAGG CUGAU | IGA X | GAA | AUGCCAUA | UAUGGCAUC CCUCGGCC |
|    | 1410 | UGUUGGCC CUGAL | iga x | GAA | AGGGAUGC | GCAUCCCUC GGCCAACA |
| 10 | 1421 | AGCCACGU CUGAU | iga x | GAA | AUUGUUGG | CCAACAAUC ACGUGGCU |
| -  | 1430 | GGGUGCCA CUGAU | iga x | GAA | AGCCACGU | ACGUGGCUC UGGCACCC |
|    | 1443 | AUUGUGGU CUGAU | ga x  | GAA | ACAGGGGU | ACCCCUGUC ACCACAAU |
|    | 1452 | UUUGGAGU CUGAU | GA X  | GAA | AUUGUGGU | ACCACAAUC ACUCCAAA |
|    | 1456 | UUUCUUUG CUGAU | GA X  | GAA | AGUGAUUG | CAAUCACUC CAAAGAAA |
| 15 | 1468 | AGAAGUCA CUGAU | GA X  | GAA | ACCUUUCU | AGAAAGGUA UGACUUCU |
|    | 1474 | CAGUGCAG CUGAU | GA X  | GAA | AGUCAUAC | GUAUGACUU CUGCACUG |
|    | 1475 | UCAGUGCA CUGAU | GA X  | GAA | AAGUCAUA | UAUGACUUC UGCACUGA |
|    | 1495 | GGAUAAAG CUGAU | GA X  | GAA | AUUCUUCA | UGAAGAAUC CUUUAUCC |
|    | 1498 | CCAGGAUA CUGAU | GA X  | GAA | AGGAUUCU | AGAAUCCUU UAUCCUGG |
| 20 | 1499 | UCCAGGAU CUGAU | GA X  | GAA | AAGGAUUC | GAAUCCUUU AUCCUGGA |
|    | 1500 | AUCCAGGA CUGAU | GA X  | GAA | AAAGGAUU | AAUCCUUUA UCCUGGAU |
|    | 1502 | GGAUCCAG CUGAU | GA X  | GAA | AUAAAGGA | UCCUUUAUC CUGGAUCC |
|    | 1509 | GCUGCUGG CUGAU | GA X  | GAA | AUCCAGGA | UCCUGGAUC CCAGCAGC |
|    | 1522 | UGUUUCCU CUGAU | GA X  | GAA | AGUUGCUG | CAGCAACUU AGGAAACA |
| 25 | 1523 | CUGUUUCC CUGAU | GA X  | GAA | AAGUUGCU | AGCAACUUA GGAAACAG |
|    | 1535 | AUGCUCUC CUGAU |       |     |          | AACAGAAUU GAGAGCAU |
|    | 1544 | CGCUGAGA CUGAU |       |     |          | GAGAGCAUC UCUCAGCG |
|    | 1546 | UGCGCUGA CUGAU |       |     |          | GAGCAUCUC UCAGCGCA |
|    | 1548 | CAUGCGCU CUGAU |       |     |          |                    |
| 30 | 1562 | CCUUCUAU CUGAU |       |     |          | AUGACGGUC AUAGAAGG |
|    | 1565 | GUUCCUUC CUGAU |       |     |          | ACGGUCAUA GAAGGAAC |
|    | 1578 | AACCGUCU CUGAU |       |     |          | GAACAAAUA AGACGGUU |
|    | 1586 | AAUGUGCU CUGAU | GA X  | GAA | ACCGUCUU | AAGACGGUU AGCACAUU |

|    | 1587 | CAAUGUGC  | CUGAUGA | . х | GAA | AACCGUCU | AGACGGUUA GCACAUUG |
|----|------|-----------|---------|-----|-----|----------|--------------------|
|    | 1594 | CCACCACC  | CUGAUGA | X   | GAA | AUGUGCUA | UAGCACAUU GGUGGUGG |
|    | 1609 | GGGUCUGA  | CUGAUGA | X   | GAA | AGUCAGCC | GGCUGACUC UCAGACCC |
|    | 1611 | AGGGGUCU  | CUGAUGA | X   | GAA | AGAGUCAG | CUGACUCUC AGACCCCU |
| 5  | 1625 | CAGCUGUA  | CUGAUGA | x   | GAA | AUUCCAGG | CCUGGAAUC UACAGCUG |
|    | 1627 | GGCAGCUG  | CUGAUGA | X   | GAA | AGAUUCCA | UGGAAUCUA CAGCUGCC |
|    | 1642 | UUUUAUUG  | CUGAUGA | x   | GAA | AGGCCCGG | CCGGGCCUU CAAUAAAA |
|    | 1643 | UUAUUUAUU | CUGAUGA | X   | GAA | AAGGCCCG | CGGGCCUUC AAUAAAAU |
|    | 1647 | CCCUAUUU  | CUGAUGA | x   | GAA | AUUGAAGG | CCUUCAAUA AAAUAGGG |
| 10 | 1652 | ACAGUCCC  | CUGAUGA | x   | GAA | UUAUUUA  | AAUAAAAUA GGGACUGU |
|    | 1673 | UAAAAUUU  | CUGAUGA | x   | GAA | AUGUUUCU | AGAAACAUA AAAUUUUA |
|    | 1678 | UGACAUAA  | CUGAUGA | x   | GAA | AUUUUAUG | CAUAAAAUU UUAUGUCA |
|    | 1679 | GUGACAUA  | CUGAUGA | x   | GAA | AAUUUUAU | AUAAAAUUU UAUGUCAC |
|    | 1680 | UGUGACAU  | CUGAUGA | x   | GAA | AAUUUUA  | UAAAAUUUU AUGUCACA |
| 15 | 1681 | CUGUGACA  | CUGAUGA | x   | GAA | AAAAUUUU | AAAAUUUUA UGUCACAG |
|    | 1685 | ACAUCUGU  | CUGAUGA | x   | GAA | ACAUAAAA | UUUUAUGUC ACAGAUGU |
|    | 1705 | AAACGUGA  | CUGAUGA | X   | GAA | AGCCAUUC | GAAUGGCUU UCACGUUU |
|    | 1706 | GAAACGUG  | CUGAUGA | X   | GAA | AAGCCAUU | AAUGGCUUU CACGUUUC |
|    | 1707 | GGAAACGU  | CUGAUGA | X   | GAA | AAAGCCAU | AUGGCUUUC ACGUUUCC |
| 20 | 1712 | UCCAAGGA  | CUGAUGA | X   | GAA | ACGUGAAA | UUUCACGUU UCCUUGGA |
|    | 1713 | UUCCAAGG  | CUGAUGA | X   | GAA | AACGUGAA | UUCACGUUU CCUUGGAA |
|    | 1714 | UUUCCAAG  | CUGAUGA | X   | GAA | AAACGUGA | UCACGUUUC CUUGGAAA |
|    | 1717 | ucuuuucc  | CUGAUGA | x   | GAA | AGGAAACG | CGUUUCCUU GGAAAAGA |
|    | 1756 | CCACACAG  | CUGAUGA | X   | GAA | ACAGUUUC | GAAACUGUC CUGUGUGG |
| 25 | 1766 | AAUUUAUU  | CUGAUGA | X   | GAA | ACCACACA | UGUGUGGUC AAUAAAUU |
|    | 1770 | CAGGAAUU  | CUGAUGA | X   | GAA | AUUGACCA | UGGUCAAUA AAUUCCUG |
|    | 1774 | UGUACAGG  | CUGAUGA | X   | GAA | AUUUAUUG | CAAUAAAUU CCUGUACA |
|    | 1775 | CUGUACAG  | CUGAUGA | X   | GAA | UUAUUUAA | AAUAAAUUC CUGUACAG |
|    | 1780 | UGUCUCUG  | CUGAUGA | X   | GAA | ACAGGAAU | AUUCCUGUA CAGAGACA |
| 30 | 1790 | AUCCAGGU  | CUGAUGA | X   | GAA | AUGUCUCU | AGAGACAUU ACCUGGAU |
|    | 1791 | AAUCCAGG  | CUGAUGA | X   | GAA | AAUGUCUC | GAGACAUUA CCUGGAUU |
|    | 1799 | CGUAGCAG  | CUGAUGA | X   | GAA | AUCCAGGU | ACCUGGAUU CUGCUACG |
|    | 1800 | CCGUAGCA  | CUGAUGA | X   | GAA | AAUCCAGG | CCUGGAUUC UGCUACGG |

PCT/US96/17480

WO 97/15662

|    | 1805 | ACUGUCCG | CUGAUGA |     | GAA | AGCAGAAU | AUUCUGCUA CGGACAGU |
|----|------|----------|---------|-----|-----|----------|--------------------|
|    | 1814 | CUGUUGUU | CUGAUGA | . X | GAA | ACUGUCCG | CGGACAGUU AACAACAG |
|    | 1815 | ucuguugu | CUGAUGA | X   | GAA | AACUGUCC | GGACAGUUA ACAACAGA |
|    | 1836 | GCUGAUAC | CUGAUGA | X   | GAA | AUGGUGCA | UGCACCAUA GUAUCAGC |
| 5  | 1839 | CUUGCUGA | CUGAUGA | X   | GAA | ACUAUGGU | ACCAUAGUA UCAGCAAG |
|    | 1841 | UGCUUGCU | CUGAUGA | X   | GAA | AUACUAUG | CAUAGUAUC AGCAAGCA |
|    | 1866 | GUAAUCUU | CUGAUGA | X   | GAA | AGUGGUGG | CCACCACUC AAGAUUAC |
|    | 1872 | GAUGGAGU | CUGAUGA | X   | GAA | AUCUUGAG | CUCAAGAUU ACUCCAUC |
|    | 1873 | UGAUGGAG | CUGAUGA | X   | GAA | AAUCUUGA | UCAAGAUUA CUCCAUCA |
| 10 | 1876 | GAGUGAUG | CUGAUGA | X   | GAA | AGUAAUCU | AGAUUACUC CAUCACUC |
|    | 1880 | UUCAGAGU | CUGAUGA | X   | GAA | AUGGAGUA | UACUCCAUC ACUCUGAA |
|    | 1884 | AAGGUUCA | CUGAUGA | X   | GAA | AGUGAUGG | CCAUCACUC UGAACCUU |
|    | 1892 | UUGAUGAC | CUGAUGA | X   | GAA | AGGUUCAG | CUGAACCUU GUCAUCAA |
|    | 1895 | UUCUUGAU | CUGAUGA | X   | GAA | ACAAGGUU | AACCUUGUC AUCAAGAA |
| 15 | 1898 | ACGUUCUU | CUGAUGA | X   | GAA | AUGACAAG | CUUGUCAUC AAGAACGU |
|    | 1909 | CUUCUAGA | CUGAUGA | X   | GAA | ACACGUUC | GAACGUGUC UCUAGAAG |
|    | 1911 | GUCUUCUA | CUGAUGA | X   | GAA | AGACACGU | ACGUGUCUC UAGAAGAC |
|    | 1913 | GAGUCUUC | CUGAUGA | X   | GAA | AGAGACAC | GUGUCUCUA GAAGACUC |
|    | 1921 | AGGUGCCC | CUGAUGA | X   | GAA | AGUCUUCU | AGAAGACUC GGGCACCU |
| 20 | 1930 | UGCACGCA | CUGAUGA | X   | GAA | AGGUGCCC | GGGCACCUA UGCGUGCA |
|    | 1952 | CCUGUGUA | CUGAUGA | X   | GAA | AUGUUCCU | AGGAACAUA UACACAGG |
|    | 1954 | CCCCUGUG | CUGAUGA | X   | GAA | AUAUGUUC | GAACAUAUA CACAGGGG |
|    | 1970 | UUCCGAAG |         |     |     |          | GAAGACAUC CUUCGGAA |
|    | 1973 | GUCUUCCG | CUGAUGA | X   | GAA | AGGAUGUC | GACAUCCUU CGGAAGAC |
| 25 | 1974 | UGUCUUCC |         |     |     |          | ACAUCCUUC GGAAGACA |
|    | 1988 | CUAACGAG |         |     |     | •        | ACAGAAGUU CUCGUUAG |
|    | 1989 | UCUAACGA |         |     |     |          | CAGAAGUUC UCGUUAGA |
|    | 1991 | UCUCUAAC |         |     |     |          | GAAGUUCUC GUUAGAGA |
|    | 1994 |          |         |     |     | ACGAGAAC | GUUCUCGUU AGAGAUUC |
| 30 | 1995 |          |         |     |     | AACGAGAA | UUCUCGUUA GAGAUUCG |
|    | 2001 |          |         |     |     | AUCUCUAA | UUAGAGAUU CGGAAGCG |
|    | 2002 |          |         |     |     | AAUCUCUA | UAGAGAUUC GGAAGCGC |
|    | 2021 | AGGUUUUG | CUGAUGA | X   | GAA | AGCAGGUG | CACCUGCUU CAAAACCU |

|    | 2022 | GAGGUUUU C  | UGAUGA | X | GAA | AAGCAGGU | ACCUGCUUC   | AAAACCUC |
|----|------|-------------|--------|---|-----|----------|-------------|----------|
|    | 2030 | UAGUCACU C  | UGAUGA | X | GAA | AGGUUUUG | CAAAACCUC   | AGUGACUA |
|    | 2038 | AGACCUCG C  | UGAUGA | X | GAA | AGUCACUG | CAGUGACUA   | CGAGGUCU |
|    | 2045 | CUGAUGGA C  | UGAUGA | X | GAA | ACCUCGUA | UACGAGGUC   | UCCAUCAG |
| 5  | 2047 | CACUGAUG C  | UGAUGA | X | GAA | AGACCUCG | CGAGGUCUC   | CAUCAGUG |
|    | 2051 | GAGCCACU C  | UGAUGA | X | GAA | AUGGAGAC | GUCUCCAUC   | AGUGGCUC |
|    | 2059 | AGGUCGUA C  | UGAUGA | X | GAA | AGCCACUG | CAGUGGCUC   | UACGACCU |
|    | 2061 | UAAGGUCG CI | UGAUGA | x | GAA | AGAGCCAC | GUGGCUCUA   | CGACCUUA |
|    | 2068 | GACAGUCU CI | JGAUGA | X | GAA | AGGUCGUA | UACGACCUU   | AGACUGUC |
| 10 | 2069 | UGACAGUC CI | JGAUGA | X | GAA | AAGGUCGU | ACGACCUUA   | GACUGUCA |
|    | 2076 | UCUAGCUU C  | JGAUGA | X | GAA | ACAGUCUA | UAGACUGUC   | AAGCUAGA |
|    | 2082 | GACACCUC CO | JGAUGA | X | GAA | AGCUUGAC | GUCAAGCUA   | GAGGUGUC |
|    | 2090 | GGCGCGGG CT | JGAUGA | X | GAA | ACACCUCU | AGAGGUGUC   | CCCGCGCC |
|    | 2100 | AGUGAUCU CU | JGAUGA | x | GAA | AGGCGCGG | ccgcgccuc   | AGAUCACU |
| 15 | 2105 | AACCAAGU CU |        |   |     |          | CCUCAGAUC   | ACUUGGUU |
|    | 2109 | UUUGAACC CI |        |   |     |          | AGAUCACUU   | GGUUCAAA |
|    | 2113 | nennnnne cr |        |   |     |          | CACUUGGUU   | CAAAAACA |
|    | 2114 | טטפטטטטט כנ |        |   |     |          | ACUUGGUUC   | AAAAACAA |
|    | 2132 | טכטטפטטפ כט |        |   |     |          | CACAAAAUA   | CAACAAGA |
| 20 | 2150 | CCUAAAAU CU |        |   |     |          | CCGGGAAUU   | AUUUUAGG |
|    | 2151 | UCCUAAAA CU |        |   |     |          | CGGGAAUUA   | UUUUAGGA |
| -  | 2153 | GGUCCUAA CU |        |   |     |          | GGAAUUAUU   | UUAGGACC |
|    | 2154 | UGGUCCUA CU |        |   |     |          | GAAUUAUUU   | UAGGACCA |
|    | 2155 | cneenccn cn | GAUGA  | X | GAA | AAAUAAUU | UUUUUAUUUAA | AGGACCAG |
| 25 | 2156 | ccuggucc cu |        |   |     |          | AUUUUUA     | GGACCAGG |
|    | 2179 | UUUCAAUA CU |        |   |     |          | CACGCUGUU   | UAUUGAAA |
|    | 2180 | CUUUCAAU CU |        |   |     |          | ACGCUGUUU   | AUUGAAAG |
|    | 2181 | UCUUUCAA CU | GAUGA  | X | GAA | AAACAGCG | CGCUGUUUA   | UUGAAAGA |
|    | 2183 | ACUCUUUC CU | GAUGA  | X | GAA | AUAAACAG | CUGUUUAUU   | GAAAGAGU |
| 30 | 2192 | טככטכטפט כט | GAUGA  | X | GAA | ACUCUUUC | GAAAGAGUC   | ACAGAGGA |
|    | 2213 | CACCUAUA CU | GAUGA  | X | GAA | ACACCCUC | GAGGGUGUC   | UAUAGGUG |
|    | 2215 | GGCACCUA CU | GAUGA  | X | GAA | AGACACCC | GGGUGUCUA   | UAGGUGCC |
|    | 2217 | UCGGCACC CU | GAUGA  | x | GAA | AUAGACAC | GUGUCUAUA   | GGUGCCGA |

PCT/US96/17480

|    | 2263 | CGGUGAGG | CUGAUGA | X   | GAA | AGGCUGCG | CGCAGCCUA   | CCUCACCG  |
|----|------|----------|---------|-----|-----|----------|-------------|-----------|
|    | 2267 | UGCACGGU | CUGAUGA | X   | GAA | AGGUAGGC | GCCUACCUC   | ACCGUGCA  |
|    | 2284 | ACUUGUCU | CUGAUGA | X   | GAA | AGGUUCCU | AGGAACCUC   | AGACAAGU  |
|    | 2293 | CCAGGUUU | CUGAUGA | . x | GAA | ACUUGUCU | AGACAAGUC   | AAACCUGG  |
| 5  | 2309 | GUGAGCGU | CUGAUGA | x   | GAA | AUCAGCUC | GAGCUGAUC   | ACGCUCAC  |
|    | 2315 | GUGCACGU | CUGAUGA | x   | GAA | AGCGUGAU | AUCACGCUC   | ACGUGCAC  |
|    | 2342 | AGCCAAAA | CUGAUGA | X   | GAA | AGGGUCGC | GCGACCCUC   | บบบบเดียด |
|    | 2344 | GGAGCCAA | CUGAUGA | x   | GAA | AGAGGGUC | GACCCUCUU   | UUGGCUCC  |
|    | 2345 | AGGAGCCA | CUGAUGA | x   | GAA | AAGAGGGU | ACCCUCUUU   | UGGCUCCU  |
| 10 | 2346 | AAGGAGCC | CUGAUGA | X   | GAA | AAAGAGGG | cccucuuuu   | GGCUCCUU  |
|    | 2351 | GUUAGAAG | CUGAUGA | X   | GAA | AGCCAAAA | uuuuggcuc   | CUUCUAAC  |
|    | 2354 | AGAGUUAG | CUGAUGA | x   | GAA | AGGAGCCA | UGGCUCCUU   | CUAACUCU  |
|    | 2355 | GAGAGUUA | CUGAUGA | X   | GAA | AAGGAGCC | GGCUCCUUC   | UAACUCUC  |
|    | 2357 | AAGAGAGU | CUGAUGA | x   | GAA | AGAAGGAG | CUCCUUCUA   | ACUCUCUU  |
| 15 | 2361 | GAUGAAGA | CUGAUGA | x   | GAA | AGUUAGAA | UUCUAACUC   | UCUUCAUC  |
|    | 2363 | CUGAUGAA | CUGAUGA | x   | GAA | AGAGUUAG | CUAACUCUC   | UUCAUCAG  |
|    | 2365 | UUCUGAUG | CUGAUGA | x   | GAA | AGAGAGUU | AACUCUCUU   | CAUCAGAA  |
|    | 2366 | UUUCUGAU | CUGAUGA | X   | GAA | AAGAGAGU | ACUCUCUUC   | AUCAGAAA  |
|    | 2369 | AGUUUUCU | CUGAUGA | x   | GAA | AUGAAGAG | CUCUUCAUC   | AGAAAACU  |
| 20 | 2386 | CGGAAGAA | CUGAUGA | x   | GAA | ACCGCUUC | GAAGCGGUC   | UUCUUCCG  |
|    | 2388 | UUCGGAAG | CUGAUGA | X   | GAA | AGACCGCU | AGCGGUCUU   | CUUCCGAA  |
|    | 2389 | CUUCGGAA | CUGAUGA | x   | GAA | AAGACCGC | GCGGUCUUC   | UUCCGAAG  |
|    | 2391 | UACUUCGG | CUGAUGA | X   | GAA | AGAAGACC | GGUCUUCUU   | CCGAAGUA  |
|    | 2392 | UUACUUCG |         |     |     |          | GUCUUCUUC   | CGAAGUAA  |
| 25 | 2399 | ucugucuu | CUGAUGA | X   | GAA | ACUUCGGA | UCCGAAGUA   | AAGACAGA  |
|    | 2410 | UUGACAGG | CUGAUGA | x   | GAA | AGUCUGUC | GACAGACUA   | CCUGUCAA  |
|    | 2416 | UAAUGAUU | CUGAUGA | X   | GAA | ACAGGUAG | CUACCUGUC . | AAUCAUUA  |
|    | 2420 |          |         |     |     | AUUGACAG | CUGUCAAUC   | AUUAUGGA  |
|    | 2423 |          |         |     |     | AUGAUUGA | UCAAUCAUU . | AUGGACCC  |
| 30 | 2424 |          |         |     |     | AAUGAUUG | CAAUCAUUA   | UGGACCCA  |
|    | 2441 |          |         |     |     | ACUUCAUC | GAUGAAGUU   | CCCCUGGA  |
|    | 2442 |          |         |     |     | AACUUCAU | AUGAAGUUC   | CCCUGGAU  |
|    | 2473 | UGGCAUCA | CUGAUGA | X   | GAA | AGGGCAGC | GCUGCCCUA   | UGAUGCCA  |

|     | 2494 | CCCGUGCA CUGAUGA X GAA ACUCCCAC | GUGGGAGUU UGCACGGG |
|-----|------|---------------------------------|--------------------|
|     | 2495 | UCCCGUGC CUGAUGA X GAA AACUCCCA | UGGGAGUUU GCACGGGA |
|     | 2516 | GAUUUGCC CUGAUGA X GAA AGUUUCAG | CUGAAACUA GGCAAAUC |
|     | 2524 | UUCCGAGC CUGAUGA X GAA AUUUGCCU | AGGCAAAUC GCUCGGAA |
| 5   | 2528 | CCUCUUCC CUGAUGA X GAA AGCGAUUU | AAAUCGCUC GGAAGAGG |
|     | 2541 | UUUCCCAA CUGAUGA X GAA AGCCCCUC | GAGGGGCUU UUGGGAAA |
|     | 2542 | CUUUCCCA CUGAUGA X GAA AAGCCCCU | AGGGGCUUU UGGGAAAG |
|     | 2543 | ACUUUCCC CUGAUGA X GAA AAAGCCCC | GGGGCUUUU GGGAAAGU |
|     | 2552 | GCUUGAAC CUGAUGA X GAA ACUUUCCC | GGGAAAGUC GUUCAAGC |
| 10  | 2555 | GAGGCUUG CUGAUGA X GAA ACGACUUU | AAAGUCGUU CAAGCCUC |
|     | 2556 | AGAGGCUU CUGAUGA X GAA AACGACUU | AAGUCGUUC AAGCCUCU |
|     | 2563 | CAAAUGCA CUGAUGA X GAA AGGCUUGA | UCAAGCCUC UGCAUUUG |
|     | 2569 | UAAUGCCA CUGAUGA X GAA AUGCAGAG | CUCUGCAUU UGGCAUUA |
|     | 2570 | UUAAUGCC CUGAUGA X GAA AAUGCAGA | UCUGCAUUU GGCAUUAA |
| 15  | 2576 | GAUUUCUU CUGAUGA X GAA AUGCCAAA | UUUGGCAUU AAGAAAUC |
|     | 2577 | UGAUUUCU CUGAUGA X GAA AAUGCCAA | JUGGCAUUA AGAAAUCA |
|     | 2584 | AGGUGGGU CUGAUGA X GAA AUUUCUUA | UAAGAAAUC ACCCACCU |
|     | 2617 | CCUCUUUC CUGAUGA X GAA ACAUCUUC | GAAGAUGUU GAAAGAGG |
|     | 2644 | GAGCUUUG CUGAUGA X GAA ACUCACUG | CAGUGAGUA CAAAGCUC |
| 20  | 2652 | GGUCAUCA CUGAUGA X GAA AGCUUUGU | ACAAAGCUC UGAUGACC |
|     | 2666 | AAGAUCUU CUGAUGA X GAA AGUUCGGU | ACCGAACUC AAGAUCUU |
|     | 2672 | UGGGUCAA CUGAUGA X GAA AUCUUGAG | CUCAAGAUC UUGACCCA |
|     | 2674 | UGUGGGUC CUGAUGA X GAA AGAUCUUG | CAAGAUCUU GACCCACA |
| 2.5 | 2684 | UGAUGGCC CUGAUGA X GAA AUGUGGGU | ACCCACAUC GGCCAUCA |
| 25  | 2691 | AUUCAGAU CUGAUGA X GAA AUGGCCGA | UCGGCCAUC AUCUGAAU |
|     | 2694 | CACAUUCA CUGAUGA X GAA AUGAUGGC | GCCAUCAUC UGAAUGUG |
|     | 2705 | AGGAGGUU CUGAUGA X GAA ACCACAUU | AAUGUGGUU AACCUCCU |
|     | 2706 | CAGGAGGU CUGAUGA X GAA AACCACAU | AUGUGGUUA ACCUCCUG |
| 30  | 2711 | GCUCCCAG CUGAUGA X GAA AGGUUAAC | GUUAACCUC CUGGGAGC |
| 30  | 2742 | CACCAUCA CUGAUGA X GAA AGGCCCUC | GAGGGCCUC UGAUGGUG |
|     | 2753 | UAUUCCAC CUGAUGA X GAA AUCACCAU | AUGGUGAUC GUGGAAUA |
|     | 2761 | AUUUGCAG CUGAUGA X GAA AUUCCACG | CGUGGAAUA CUGCAAAU |
| *   | 2770 | GGUUUCCG CUGAUGA X GAA AUUUGCAG | CUGCAAAUA CGGAAACC |
|     |      |                                 |                    |

PCT/US96/17480 WO 97/15662

167 .

|    | 2782 | GGUAGUUG  | CUGAUGA | X | GAA | ACAGGUUU | AAACCUGUC   | CAACUACC |
|----|------|-----------|---------|---|-----|----------|-------------|----------|
|    | 2788 | UCUUGAGG  | CUGAUGA | X | GAA | AGUUGGAC | GUCCAACUA   | CCUCAAGA |
|    | 2792 | UUGCUCUU  | CUGAUGA | X | GAA | AGGUAGUU | AACUACCUC   | AAGAGCAA |
|    | 2809 | GACAGAAU  | CUGAUGA | X | GAA | AGUCACGU | ACGUGACUU   | AUUCUGUC |
| 5  | 2810 | AGACAGAA  | CUGAUGA | X | GAA | AAGUCACG | CGUGACUUA   | บบตบเ    |
|    | 2812 | UGAGACAG  | CUGAUGA | X | GAA | AUAAGUCA | UGACUUAUU   | CUGUCUCA |
|    | 2813 | UUGAGACA  | CUGAUGA | X | GAA | AAUAAGUC | GACUUAUUC   | UGUCUCAA |
|    | 2817 | CUUGUUGA  | CUGAUGA | X | GAA | ACAGAAUA | UAUUCUGUC   | UCAACAAG |
|    | 2819 | UCCUUGUU  | CUGAUGA | X | GAA | AGACAGAA | UUCUGUCUC   | AACAAGGA |
| 10 | 2836 | CCAUAUGC  | CUGAUGA | X | GAA | AGGCUGCG | CGCAGCCUU   | GCAUAUGG |
|    | 2841 | GAGCUCCA  | CUGAUGA | x | GAA | AUGCAAGG | CCUUGCAUA   | UGGAGCUC |
|    | 2849 | ນດວນນດດນາ | CUGAUGA | X | GAA | AGCUCCAU | AUGGAGCUC   | aagaaaga |
|    | 2900 | ACACUGUC  | CUGAUGA | X | GAA | AGGCGGGG | CCCCGCCUA   | GACAGUGU |
|    | 2909 | GAGCUGCU  | CUGAUGA | X | GAA | ACACUGUC | GACAGUGUC   | AGCAGCUC |
| 15 | 2917 | UGACACUU  | CUGAUGA | X | GAA | AGCUGCUG | CAGCAGCUC   | AAGUGUCA |
|    | 2924 | GAGCUGGU  | CUGAUGA | x | GAA | ACACUUGA | UCAAGUGUC . | ACCAGCUC |
|    | 2932 | GGAAGCUG  | CUGAUGA | X | GAA | AGCUGGUG | CACCAGCUC   | CAGCUUCC |
|    | 2938 | CUUCAGGG  | CUGAUGA | X | GAA | AGCUGGAG | CUCCAGCUU   | CCCUGAAG |
|    | 2939 | UCUUCAGG  | CUGAUGA | X | GAA | AAGCUGGA | UCCAGCUUC   | CCUGAAGA |
| 20 | 2982 | CUCACUGU  | CUGAUGA | X | GAA | AUCCUCGU | ACGAGGAUU . | ACAGUGAG |
|    | 2983 | UCUCACUG  | CUGAUGA | X | GAA | AAUCCUCG | CGAGGAUUA   | CAGUGAGA |
|    | 2993 | UGCUUGGA  | CUGAUGA | X | GAA | AUCUCACU | AGUGAGAUC 1 | UCCAAGCA |
|    | 2995 | GCUGCUUG  | CUGAUGA | X | GAA | AGAUCUCA | UGAGAUCUC   | CAAGCAGC |
|    | 3008 | UCCAUGGU  | CUGAUGA | X | GAA | AGGGGCUG | CAGCCCCUC   | ACCAUGGA |
| 25 | 3026 | CUGUAGGA  | CUGAUGA | X | GAA | AUCAGGUC | GACCUGAUU 1 | UCCUACAG |
|    | 3027 | ACUGUAGG  | CUGAUGA | X | GAA | AAUCAGGU | ACCUGAUUU ( | CCUACAGU |
|    | 3028 | AACUGUAG  | CUGAUGA | X | GAA | AAAUCAGG | CCUGAUUUC   | CUACAGUU |
|    | 3031 | GGAAACUG  | CUGAUGA | X | GAA | AGGAAAUC | GAUUUCCUA   | CAGUUUCC |
|    | 3036 | CACUUGGA  | CUGAUGA | X | GAA | ACUGUAGG | CCUACAGUU   | UCCAAGUG |
| 30 | 3037 | CCACUUGG  | CUGAUGA | X | GAA | AACUGUAG | CUACAGUUU   | CCAAGUGG |
|    | 3038 | GCCACUUG  | CUGAUGA | X | GAA | AAACUGUA | UACAGUUUC   | CAAGUGGC |
|    | 3061 | AGGACAGA  | CUGAUGA | X | GAA | ACUCCAUG | CAUGGAGUU 1 | ncnenccn |
|    | 3062 | GAGGACAG  | CUGAUGA | X | GAA | AACUCCAU | AUGGAGUUU ( | CUGUCCUC |
|    |      |           |         |   |     |          |             |          |

| 3067 UUCUGGGG CUGAUGA X GAA ACAGAAAC 3070 ACUUUCUG CUGAUGA X GAA AGGACAGA UCUGUCCUC CO 3083 UCCCGAUG CUGAUGA X GAA AUGCACUU AAGUGCAUU CA 3084 GUCCCGAU CUGAUGA X GAA AUGCACUU AGUGCAUUC A 3087 CAGGUCCC CUGAUGA X GAA AUGCACUU AGUGCAUUC A 3110 GAUAAAAG CUGAUGA X GAA AUGUUUCUU AGAAACAUC CC 3111 UCAGAUAA CUGAUGA X GAA AAGGAUGUU AACAUCCUUU UI 3114 CUCAGAUU CUGAUGA X GAA AAGGAUGUU AACAUCCUUU UI 3116 UUCUCAGAU CUGAUGA X GAA AAAGGAUGU ACAUCCUUUU AI 3118 UGUUCUCA CUGAUGA X GAA AAAAGGAUG CCUUUUUAUC UI 3114 AAGUCGCC CUGAUGA X GAA AUAAAAGG CCUUUUUAUC UI 3140 AAGUCGCA CUGAUGA X GAA AUCUUCAC GUGAAGAUU UI 3141 AAAGUCGC CUGAUGA X GAA AAUCUUCAC GUGAAGAUU UI 3141 AAAGUCGC CUGAUGA X GAA AAUCUUCAC GUGAAGAUU UI 3149 GCCAGGCC CUGAUGA X GAA AAUCUUCAC UIGAAGAUU UI 3149 GCCAGGCC CUGAUGA X GAA AAUCUCCGG CCCGGGAUAU UI 3165 CUUAUAAA CUGAUGA X GAA AAUCUCCGG CCCGGGAUAU UI 3166 GUUCUUAU CUGAUGA X GAA AUAUCCCC GGGAUAUUU AI 3168 GUUCUUAU CUGAUGA X GAA AUAUCCCC GGGAUAUUU AI 3171 AGGGUUCU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AI 3183 CCUCACAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AI 3184 UCCUCACA CUGAUGA X GAA AAUAAUCCC GGGAUAUUU AI 3185 CCUCACAU CUGAUGA X GAA AUAAAUAU 3186 GUUCUUAC CUGAUGA X GAA AUAAAUAU 3187 AAGUCGAC CUGAUGA X GAA AUAAAUAUC 3188 GGGAAGUC CUGAUGA X GAA AUAAAUAU 3189 GCUCAGAC CUGAUGA X GAA AUAAAUAUC 3180 GGGAAGUC CUGAUGA X GAA AUAAAUAUC 3180 GGGAAGUC CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3180 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3181 UCCUCACA CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3181 UCCUCACA CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3180 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUUA COC 3200 UUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU COC 3210 UUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU COC 3211 AUCCAUCUU CUGAUGA X GAA AGGGGAAG CUCCGACUU COC 3212 UUUAGGG CUGAUGA X GAA AGGCAUCC GGAUGAUCC GAC 3228 GGAUUCAG CUGAUGA X GAA AGGCAUCC GGAUGGCU CUCGACUU COC 3221 UUUCUGAAC CUGAUGA X GAA AGGCAUCC GGAUGGCU CUCGACUU COC 3221 CUCGACUU CUGAUGA X GAA AGGAUGGAU CUCCGCUA AAA 3223 UUGCCAAC CUGAUGA X GAA AGGAUGGAU AUCCAUCUU UGA                                   |     |      |                                 |                    |
|--|-----|------|---------------------------------|--------------------|
| 3067 UUCUGGGG CUGAUGA X GAA ACAGAAAC 3070 ACUUUCUG CUGAUGA X GAA AGGACAGA UCUGUCCUC CO 3083 UCCCGAUG CUGAUGA X GAA AUGCACUU AAGUGCAUU CA 3084 GUCCCGAU CUGAUGA X GAA AUGCACUU AGUGCAUUC A 3087 CAGGUCCC CUGAUGA X GAA AUGCACUU AGUGCAUUC A 3110 GAUAAAAG CUGAUGA X GAA AUGUUUCUU AGAAACAUC CC 3111 UCAGAUAA CUGAUGA X GAA AAGGAUGUU AACAUCCUUU UI 3114 CUCAGAUU CUGAUGA X GAA AAGGAUGUU AACAUCCUUU UI 3116 UUCUCAGAU CUGAUGA X GAA AAAGGAUGU ACAUCCUUUU AI 3118 UGUUCUCA CUGAUGA X GAA AAAAGGAUG CCUUUUUAUC UI 3114 AAGUCGCC CUGAUGA X GAA AUAAAAGG CCUUUUUAUC UI 3140 AAGUCGCA CUGAUGA X GAA AUCUUCAC GUGAAGAUU UI 3141 AAAGUCGC CUGAUGA X GAA AAUCUUCAC GUGAAGAUU UI 3141 AAAGUCGC CUGAUGA X GAA AAUCUUCAC GUGAAGAUU UI 3149 GCCAGGCC CUGAUGA X GAA AAUCUUCAC UIGAAGAUU UI 3149 GCCAGGCC CUGAUGA X GAA AAUCUCCGG CCCGGGAUAU UI 3165 CUUAUAAA CUGAUGA X GAA AAUCUCCGG CCCGGGAUAU UI 3166 GUUCUUAU CUGAUGA X GAA AUAUCCCC GGGAUAUUU AI 3168 GUUCUUAU CUGAUGA X GAA AUAUCCCC GGGAUAUUU AI 3171 AGGGUUCU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AI 3183 CCUCACAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AI 3184 UCCUCACA CUGAUGA X GAA AAUAAUCCC GGGAUAUUU AI 3185 CCUCACAU CUGAUGA X GAA AUAAAUAU 3186 GUUCUUAC CUGAUGA X GAA AUAAAUAU 3187 AAGUCGAC CUGAUGA X GAA AUAAAUAUC 3188 GGGAAGUC CUGAUGA X GAA AUAAAUAU 3189 GCUCAGAC CUGAUGA X GAA AUAAAUAUC 3180 GGGAAGUC CUGAUGA X GAA AUAAAUAUC 3180 GGGAAGUC CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3180 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3181 UCCUCACA CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3181 UCCUCACA CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UIG 3180 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUUA COC 3200 UUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU COC 3210 UUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU COC 3211 AUCCAUCUU CUGAUGA X GAA AGGGGAAG CUCCGACUU COC 3212 UUUAGGG CUGAUGA X GAA AGGCAUCC GGAUGAUCC GAC 3228 GGAUUCAG CUGAUGA X GAA AGGCAUCC GGAUGGCU CUCGACUU COC 3221 UUUCUGAAC CUGAUGA X GAA AGGCAUCC GGAUGGCU CUCGACUU COC 3221 CUCGACUU CUGAUGA X GAA AGGAUGGAU CUCCGCUA AAA 3223 UUGCCAAC CUGAUGA X GAA AGGAUGGAU AUCCAUCUU UGA                                   |     | 3063 | GGAGGACA CUGAUGA X GAA AAACUCCA | UGGAGUUUC UGUCCUCC |
| 3070 ACUUUCUG CUGAUGA X GAA AGGACAGA UCUGUCCUC CO 3083 UCCCGAUG CUGAUGA X GAA AUGCACUU AAGUGCAUU CA 3087 CAGGUCCC CUGAUGA X GAA AUGCACUU AGUGCAUUC A 3087 CAGGUCCC CUGAUGA X GAA AUGAAUGC GCAUUCAUC G 3110 GAUAAAAG CUGAUGA X GAA AUGUUUCU AGAAACAUC CO 3111 UCAGAUA CUGAUGA X GAA AAGGAUGUU ACAUCCUUU UI 3114 CUCAGAUA CUGAUGA X GAA AAAGGAUGU ACAUCCUUU UI 3116 UUCUCAGA CUGAUGA X GAA AAAAGGAUG CAUCCUUUU AI 3118 UGUUCUCA CUGAUGA X GAA AAAAGGAU AUCCUUUUA UI 3110 AAGUCGCC CUGAUGA X GAA AAAAGGAU AUCCUUUUA UI 3111 UUCUCAGA CUGAUGA X GAA AAAAGGAU AUCCUUUUA UI 3111 AAAGUCGC CUGAUGA X GAA AUCUUCAC GUGAAGAUU UI 3114 AAAGUCGC CUGAUGA X GAA AAUCUUCAC GUGAAGAUU UI 3114 AAAGUCGC CUGAUGA X GAA AAUCUUCAC UIGAAGAUUU UI 3114 AAAGUCGC CUGAUGA X GAA AAUCUUCAC UIGAAGAUUU UI 3114 AAAGUCGC CUGAUGA X GAA AAUCUUCAC UIGAAGAUUU UI 3116 CUUAUAAA CUGAUGA X GAA AAUCUCCGGG CCCCGGGAUA UI 3165 CUUAUAAA CUGAUGA X GAA AUCUCCGGG CCCCGGGAUAU UI 3166 GUUCUUAU CUGAUGA X GAA AUCUCCGGG CCCCGGGAUAU UI 3168 GUUCUUAU CUGAUGA X GAA AUAUCCCC GGGAUAUUU UIA 3117 AGGGUUCU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3183 CCUCACAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3184 UCCUCACA CUGAUGA X GAA AUAAAUAU AUAUUUAUA ACG 3184 UCCUCACA CUGAUGA X GAA AUAAAUAU AUAUUUAUA ACG 3184 UCCUCACA CUGAUGA X GAA AUAAAUAU ACCCUGAUUU UIGAAGGGU CCCCGAUUU GAAGAAUU CUGAUGA X GAA AUAAAUAU ACCCUGAUUU AUA 3183 CCUCACAU CUGAUGA X GAA AUAAAUAU ACCCUGACUU CCCCUGAUUA UIGAAGAGAU CUCAACAU CUGAUGA X GAA AUAAAUAU ACCCUGACUU CCCCUGAUUA UIGAAGAGA CUCAACAU CUGAUGA X GAA AUCACGGG CCCCGGAUAUU AUA 3184 UCCUCACA CUGAUGA X GAA AUCACGGG CCCCGGAUAUU ACCCUGACUU CCCCUGAUUA CCCCCUGAUUA CCCCCUGAUUA CCCCCUGAUUA CCCCCUGAUUA CCCCCUGAUUA CCCCCCUGAUUA CCCCCUGAUUA CCCCCCUGAUUA CCCCCCUGAUUA CCCCCCUGAUUA CCCCCCUGAUUA CCCCCCUA AAA 3220 UUUAGGGG CUGAUGA X GAA AGCCAUCC GGAUGGCU CCCCCUA AAA 32210 UUUAGGGG CUGAUGA X GAA AGCCAUCC GGAUGGCU CCCCCUAACAU CUGAUGA X GAA AGCCAUCC GGAUGGCU CCCCCUAACAU CCCCCUAACAAC CUGAUGA X GAA AGCCAUCC GGAUGGCU CCCCCUAACAAC CUGAUGA X GAA AGCAUGGAU CCCCCCUAACAC CUGAUGA X GAA AGUCGAUC GAAUCCCUC CCCCCAACAU CUGAUGA X |     | 3067 | UUCUGGAG CUGAUGA X GAA ACAGAAAC | GUUUCUGUC CUCCAGAA |
| 3083 UCCCGAUG CUGAUGA X GAA AUGCACUU AAGUGCAUU CAGUGCAUU CUGAUGA X GAA AAUGCACUU AGUGCAUUC AAGUGCAUUC AAGUGCAUUC AAGUGCAUUC AAGAACAUC CUGAUGA X GAA AUGCACUU AAGAACAUC CUGAUGA X GAA AUGUUUCUU AAGAACAUC CUGAUGA X GAA AAGGAUGUU AACAUCCUUU UU AAGAACAUC CUGAUGA X GAA AAGGAUGUU AACAUCCUUU UU AAGAACAUC CUGAUGA X GAA AAAGGAUGU AACAUCCUUU UU AAGAACAUC CUGAUGA X GAA AAAGGAUGU AACAUCCUUU UU AAGAACAUC CUGAUGA X GAA AAAAGGAUG CAUCCUUUUU AAGAACAUC CUGAUGA X GAA AAAAGGAU AUCCUUUUAUC UGAAGAAUU UGAAGAAUAU UGAAGAAUAU CUGAUGA X GAA AAUCUCCG CCCGGGAUAU UU AAGAAGGAU UUGAAGAA X GAA AAUAUCCCG CCCGGGAUAUU UAAGAAGAUU UGAAGAAUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AUAAAAGG CCUUGAUGA X GAA AAUAUCCC GGGAUAUUU AAGAAGAUU UGAAGAA X GAA AAUAUCCC GGGAUAUUU AAGAAGAUU UAAGAAGAUU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AAGAAGAUU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AAGAAGAUAU CUGAUGA X GAA AAUAUCCC GAGAUAUUU AUAAAAUAU AAGAAGAAUAUCC GAGAAAUUU CUGAUGA X GAA AAUAAUCCC GAGAAAUUU AAGAAGAA AAUAAUCCC GAGAAAUUU AAGAAGAAGAAAUAUCCC GAGAAAUAU AACCCGAAAAUAUCCCAAACCAAA  |     | 3070 | ACUUUCUG CUGAUGA X GAA AGGACAGA | UCUGUCCUC CAGAAAGU |
| 3087 CAGGUCCC CUGAUGA X GAA AUGAAUGC  3110 GAUAAAAG CUGAUGA X GAA AUGUUUCU  3111 UCAGAUAA CUGAUGA X GAA AGGAUGU  3111 UCAGAUAA CUGAUGA X GAA AGGAUGU  3111 UCUCAGAU CUGAUGA X GAA AAAGGAUGU  3111 UCUCAGAU CUGAUGA X GAA AAAAGGAUG  3111 UCUCAGAU CUGAUGA X GAA AAAAGGAUG  3111 UCUCAGAU CUGAUGA X GAA AAAAGGAUG  3111 UUCUCAGAU CUGAUGA X GAA AAAAGGAU  3111 UUCUCAGAU CUGAUGA X GAA AAAAAGGAU  3111 UGUUCUCA CUGAUGA X GAA AUAAAAGG  3111 AAAGUCGC CUGAUGA X GAA AUCUUCAC  3111 AAAGUCGC CUGAUGA X GAA AUCUUCAC  3112 GCCAGGCCA CUGAUGA X GAA AAUCUUCA  3113 GCCAGGCCA CUGAUGA X GAA AUCUUCAC  3114 AAAGUCGC CUGAUGA X GAA AAUCUUCA  3149 GCCAGGCCA CUGAUGA X GAA AUCCCGGG  3149 GCCAGGCC CUGAUGA X GAA AUCCCCGGG  3140 UUCUUAUA CUGAUGA X GAA AUCCCCGGG  3140 GUUCUUAU CUGAUGA X GAA AUAUCCCC  3146 GUUCUUAU CUGAUGA X GAA AUAUCCCC  3146 GUUCUUAU CUGAUGA X GAA AAUAUCCC  3147 AGGGUUCU CUGAUGA X GAA AAUAUCCC  3148 GGUUCUUA CUGAUGA X GAA AAUAUCCC  3149 GGUUCUUA CUGAUGA X GAA AAUAUCCC  3140 GGGAUAUUU AUA  3151 AGGGUUCU CUGAUGA X GAA AAUAAUAU  3151 AGGGUUCU CUGAUGA X GAA AAUAAUAU  3164 UCCUCACA CUGAUGA X GAA AAUAUCCC  3165 GGUUCUUA CUGAUGA X GAA AUCAGGGU  3166 GGGAAGUC CUGAUGA X GAA AUCAGGGU  3167 AGGUCGAC CUGAUGA X GAA AUCAGGGU  3168 CCCCUGAUUA UGA  3171 AGGGUUCU CUGAUGA X GAA AUCAGGGU  3180 CCCCUGAUUA UGA  3181 UCCUCACA CUGAUGA X GAA AUCAGGGU  3180 CCCCUGAUUA CUGAUGA X GAA AGUCGAGU  3180 UUUUAGGG CUGAUGA X GAA AGUCGAGU  3180 UUUUAGGG CUGAUGA X GAA AGUCGAGU  3200 UUUAGGGG CUGAUGA X GAA AGUCGAGU  3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU  3211 AUCCAUUU CUGAUGA X GAA AGUCGAGU  32228 GGAUUCAG CUGAUGA X GAA AGUCGAGU  3228 GGAUUCAG CUGAUGA X GAA AGUCGAGA  3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC  3239 UUGUCAAA CUGAUGA X GAA AGUCGAGU  3241 CCCUUGUCA CUGAUGA X GAA AGUCGAGU  3241 CCCUUGUCA CUGAUGA X GAA AGUCGAGU  3241 CCCUUGAAUC CUGAUGA X GAA AGUCGAGU  3241 CCCUUGUCA CUGAUGA X GAA AGUCGAGU  AUCCCUUUU UGA  |     | 3083 | UCCCGAUG CUGAUGA X GAA AUGCACUU | AAGUGCAUU CAUCGGGA |
| 3087 CAGGUCCC CUGAUGA X GAA AUGAAUGC  3110 GAUAAAAG CUGAUGA X GAA AUGUUUCU AGAAACAUC CO 3111 UCAGAUAA CUGAUGA X GAA AGGAUGUU AACAUCCUUU UI 3114 CUCAGAUA CUGAUGA X GAA AAGGAUGU ACAUCCUUU UI 3115 UCUCAGAU CUGAUGA X GAA AAAGGAUG CAUCCUUUU AI 3116 UUCUCAGA CUGAUGA X GAA AAAAGGAUG CCUUUUUAUC CO 3118 UGUUCUCA CUGAUGA X GAA AAAAGGAU AUCCUUUUUAUC CO 3114 AAAGUCGCA CUGAUGA X GAA AAAAAGGAU GCUGAAGAUU CO 3144 AAAGUCGC CUGAUGA X GAA AAUCUUCAC GUGAAGAUU UG 3149 GCCAGGCC CUGAUGA X GAA AAUCUUCA UGAAGAUUU GC 3149 GCCAGGCC CUGAUGA X GAA AAUCUUCA UGAAGAUUU GG 3165 CUUAUAAA CUGAUGA X GAA AAUCCCGGG CCCGGGAUA UU 3167 UUCUUAUA CUGAUGA X GAA AUAUCCCG GGGAUAUUU AU 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3169 GGUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3183 CCUCACAU CUGAUGA X GAA AAUAUCCC GGAUAUUU AU 3184 UCCUCACA CUGAUGA X GAA AAUAACCC GGAUAUUU AU 3185 CCUCACAU CUGAUGA X GAA AAUAAUCC GGAUAUUU AU 3186 GUUCUUAC CUGAUGA X GAA AAUAAUCC GGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AAUAAUCC GGAUAUUU AU 3180 GGGAUGUC CUGAUGA X GAA AAUCAGGG CCCUGAUUA UG 3181 UCCUCACA CUGAUGA X GAA AAUCAGGG CCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AAUCAGGG CCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AAUCACGG CCCUGAUUA UG 3210 UUUUAGGG CUGAUGA X GAA AGUCCGAG CUCGACUU CCC 3228 GGAUUCAG CUGAUGA X GAA AGUCGAG CUCGACUU CCC 3228 GGAUUCAG CUGAUGA X GAA AGUCGAG CUCCGCCUA AAA 3229 UUUAGGGG CUGAUGA X GAA AGUCGAG CUCCGCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGGCAAUC GGAUGCCC CUGAUGA CUGAUGA X GAA AGUCAGGA CUCCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGGCAAUC GGAUGCCC CUGAUUA CUCCCCUA AAA 3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGCCC CUCGAUUC CCC 3239 UUGUCAAA CUGAUGA X GAA AGGCAAUC GAACCAUC GGAUGCCC CUGAUGA X GAA AGUCAGGA CUCCCCUA AAA 3239 UUGUCAAA CUGAUGA X GAA AGUCAGGA CUCCCCUA AAA 3239 UUGUCAAA CUGAUGA X GAA AGGCAUCC GAAUCCAUC UUCCCCUA AAA 3241 CCUUGUCA CUGAUGA X GAA AGGCAUCC GAAUCCAUC UUCCCCUA AAA 3239 UUGUCAAA CUGAUGA X GAA AGUCAGGA AUCCCAUCU UUCA  | 5   | 3084 | GUCCCGAU CUGAUGA X GAA AAUGCACU | AGUGCAUUC AUCGGGAC |
| 3110 GAUAAAAG CUGAUGA X GAA AUGUUUCU AGAAACAUC CU 3113 UCAGAUAA CUGAUGA X GAA AGGAUGUU AACAUCCUU UI 3114 CUCAGAUA CUGAUGA X GAA AAGGAUGU ACAUCCUUU UI 3115 UCUCAGAU CUGAUGA X GAA AAAGGAUG CAUCCUUUU AI 3116 UUUCUCAGA CUGAUGA X GAA AAAAGGAU AUCCUUUUU AI 3118 UGUUCUCA CUGAUGA X GAA AAAAGGAU AUCCUUUUA UI 31140 AAGUCGCA CUGAUGA X GAA AUAAAAGG CCUUUUAUC UI 3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC GUGAAGAUU UI 3149 GCCAGGCC CUGAUGA X GAA AAUCUUCA UGAAGAUUU GI 3149 GCCAGGCC CUGAUGA X GAA AAUCUUCA UGCGACUUU GI 3165 CUUAUAAA CUGAUGA X GAA AAUCUCCG CGGGAUAUU UI 3166 GUUCUUAU CUGAUGA X GAA AUAUCCCC GGGAUAUU UI 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3169 GGUUCUUA CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3181 CCUCACAU CUGAUGA X GAA AAUAAUCC GGAUAUUU AU 3181 CCUCACAU CUGAUGA X GAA AUAAAUAU 3183 CCUCACAU CUGAUGA X GAA AUAAAUAU 3184 UCCUCACA CUGAUGA X GAA AUAAAUAU 3201 AAGUCGAG CUGAUGA X GAA AUAACGGG CCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUC 3209 UUUAGGGG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU ACCCCGACUUC COC 3221 AUCCAUUU CUGAUGA X GAA AGUCGAGU ACCCCGACUUC COC 3222 GGAAUUCAG CUGAUGA X GAA AGUCGAGG CUCGACUUC COC 3223 AUCCAUUU CUGAUGA X GAA AGUCGAGG CUCCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGUCGAGG CUCCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGUCGAGG CUCCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGUCGAGU CUCCCCUA AAA 3229 UUGUCAAAA CUGAUGA X GAA AGUCGAGU CUCCCCUA AAA 3229 UUGUCAAA CUGAUGA X GAA AGUCGAGU CUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGUCGAGU CUCCCCUA AAA 3229 UUGUCAAAA CUGAUGA X GAA AGUCGAGU CUCCCCUA AAA 3229 UUGUCAAAA CUGAUGA X GAA AGUCGAGU CUCCCCUA AAA 3239 UUGUCAAAA CUGAUGA X GAA AGUCGAGU AUCCAUCCU UGAAUCCAUC UUCCACAAUCC GAAUCCAUC UGAUGA X GAA AGUCGAUCC GAAUCCAUC UCCAAUCCAUCCU GAAUCCAUCU UUCAAUCAAA CUGAUGA X GAA AGUCGAUCC GAAUCCAUCU UUCAAACAA CUGAUGA X GAA AGUGGAUUC GAAUCCAUCU UCCAAAUCCAUCUUCAAA CUGAUGA X |     | 3087 | CAGGUCCC CUGAUGA X GAA AUGAAUGC | GCAUUCAUC GGGACCUG |
| 3113 UCAGAUAA CUGAUGA X GAA AGGAUGUU ACAUCCUUU UI 3114 CUCAGAUA CUGAUGA X GAA AAGGAUGU ACAUCCUUU UI 3115 UCUCAGAU CUGAUGA X GAA AAAGGAUG CAUCCUUUU AI 3116 UUCUCAGA CUGAUGA X GAA AAAAGGAU AUCCUUUUU AI 3118 UGUUCUCA CUGAUGA X GAA AUAAAAGG CCUUUUUAUC UI 3140 AAGUCGCA CUGAUGA X GAA AUAAAAGG CCUUUUUAUC UI 3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC GUGAAGAUU UI 3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC UGAAGAUUU GI 3149 GCCAGGCC CUGAUGA X GAA AAUCUUCA UGAAGAUUU GI 3165 CUUAUAAA CUGAUGA X GAA AAGUCGCAA UUGCGACUU UI 3166 GUUCUUAU CUGAUGA X GAA AUCCCGGG CCCGGGAUAUU UI 3168 GUUCUUAU CUGAUGA X GAA AUAUCCCC GGGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AUAAAUAUC GGAUAUUUA AU 3183 CCUCACAU CUGAUGA X GAA AUAAAUAU 3184 UCCUCACA CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UI 3185 CCUCACAU CUGAUGA X GAA AUCAGGGU CCCUGAUUA UI 3186 GUUCUUAU CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UI 3187 AGGGUUCU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AU 3188 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AU 3189 UUCUUAGGG CUGAUGA X GAA AUCAGGGU CCCUGAUUA UI 3180 CCUCACAU CUGAUGA X GAA AUCAGGGU CCCUGAUUA UI 3181 UCCUCACA CUGAUGA X GAA AUCAGGGU CCCUGAUUA UI 3181 CCUCACAU CUGAUGA X GAA AUCAGGG CCCUGAUUA UI 3181 CCUCACAU CUGAUGA X GAA AUCAGGGU CCCUGAUUA UI 3180 CCUCACAU CUGAUGA X GAA AUCACGGG CCCUGAUUA UI 3180 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCCUGAUU CCC 3201 UUUAGGGG CUGAUGA X GAA AGUCGAG CUCCACUU CCC 3210 UUUAGGGG CUGAUGA X GAA AGUCGAG CUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGUCAGGA CUCCCCUCA AAA 3228 GGAUUCAG CUGAUGA X GAA AGUCAGGA CUCCCCUCA AAA 3239 UUGUCAAA CUGAUGA X GAA AGUCAGGA CUCCCCUCA AAA 3241 CCUUGUCA CUGAUGA X GAA AGUCGAUC GAAUCCUU UGA   |     | 3110 | GAUAAAAG CUGAUGA X GAA AUGUUUCU | AGAAACAUC CUUUUAUC |
| 3115 UCUCAGAU CUGAUGA X GAA AAAGGAUG  3116 UUCUCAGA CUGAUGA X GAA AAAAGGAU  3118 UGUUCUCA CUGAUGA X GAA AAAAGGAU  31140 AAGUCGC CUGAUGA X GAA AUCUUCAC  3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC  3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC  3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC  3149 GCCAGGCC CUGAUGA X GAA AAUCUUCAC  3165 CUUAUAAA CUGAUGA X GAA AAUCUCGGG CCCGGGAUAUU UAC  3166 GUUCUUAU CUGAUGA X GAA AUAUCCCG CGGAUAUUU AUCUGAUGA X GAA AUAUCCCG CGGGAUAUUU AUCUGAUGA X GAA AAUAUCCC GGGAUAUUU AUCUGAUGA X GAA AUAUCCCG GGAUAUUU AUCUGAUGA X GAA AAUAUCCC GGAUAUUU AUCUGAUGA X GAA AUAUAUCCC GGAUAUUU AUCUGAUGA X GAA AUAAAUAU AUAUUUAUA AGAAAAUAU AUAUUUAUA AGAAAUAU AUAUUUAUA AGAAAUAU AUAUUUAUA AGAAAUAU AUAUUUAUA AGAAAUAUCCC GGAAUAUUU AUCUGAUGA X GAA AUACAGGG CCCUGAUUA UGGAGAAAAUAUCCC GGAAUAUUU AUCUGAUGA X GAA AUCAGGGU ACCCUGAUUA UGGAAAAUAU AUAUUUAUA AGAAAUAU AUAUUUAUA AGAAAUAU AUAUUUAUA AGAAAUAU AUAUUUAUA AGAAAUAU AAAUAUCCC GAAAAUAUCCC GAAAAUAUCCC GAAAAUAUCCC GAAAAUAUCCC GAAAAUAUCCC GAAAAAUAUCCC GAAAAUAUCCC GAAAAUAUCCC GAAAAUAUCCC GAAGAAAUAUCCC GAAGAAAUAUCCC GAAGAAAUAUCCC GAAGAAAUAUCCC GAAGAAAUCCCCCGAAUAU AUCUCCACCA CUGAUGA X GAA AUCCACGGC CCCUGAUUA UGGAAAAUAU AUAUUUAUA AGAAAUAU AAAUAUAU AUAUUUAUA AGAAAUAU AAAUAUAU AUAUUUAUA AGAAAUAUCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCCCGAAUACCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCC GAAGAAAUCCCCCCUAAAAAAUAUCCCCCCUAAAAAAUAUCCCCCC  |     | 3113 | UCAGAUAA CUGAUGA X GAA AGGAUGUU | AACAUCCUU UUAUCUGA |
| 3116 UUCUCAGA CUGAUGA X GAA AAAGGAU  3118 UGUUCUCA CUGAUGA X GAA AUAAAAGG  3140 AAGUCGCA CUGAUGA X GAA AUAAAAGG  3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC  3141 AAAGUCGC CUGAUGA X GAA AUCUUCAC  3148 CCAGGCCA CUGAUGA X GAA AACUUCAC  3149 GCCAGGCC CUGAUGA X GAA AAGUCGCAA  3165 CUUAUAAA CUGAUGA X GAA AAGUCGCA  3166 GUUCUUAU CUGAUGA X GAA AUCUCCGGG  3167 UUCUUAUA CUGAUGA X GAA AUAUCCCC  3168 GUUCUUAU CUGAUGA X GAA AUAUCCCC  3169 GGUUCUUA CUGAUGA X GAA AUAUCCCC  3171 AGGGUUCU CUGAUGA X GAA AUAAAUAU  3183 CCUCACAU CUGAUGA X GAA AUAAAUAU  3184 UCCUCACA CUGAUGA X GAA AUAACGGGU  3201 AAGUCGAC CUGAUGA X GAA AUCCGGG  CCCUGAUUA UGAUGA X GAA AUAACAGGG  3201 AAGUCGAC CUGAUGA X GAA AUCCAGGG  3201 UUUUAGGG CUGAUGA X GAA AUCCCCCC  3202 UUUUAGGG CUGAUGA X GAA AUCCCCCC  3203 AAGUCGAC CUGAUGA X GAA AUCCCCCC  3204 GGGAAGUC CUGAUGA X GAA AUCCCCCC  3205 GGAUAUUU CUGAUGA X GAA AUCCCCCC  3206 GGGAAGUC CUGAUGA X GAA AUCCCCCC  3207 UUUUAGGG CUGAUGA X GAA AUCCCCCC  3208 GGAUACCC CUGAUGA X GAA AGUCCCCC  3209 UUUUAGGG CUGAUGA X GAA AGUCCCCCC  3215 AUCCAUUU CUGAUGA X GAA AGUCCGAG  3228 GGAUCCAG CUGAUGA X GAA AGUCCAGC  3228 GGAUCCAG CUGAUGA X GAA AGUCCAGC  3228 GGAUCCAG CUGAUGA X GAA AGCCAUCC  GGAUGGCCC CUGAUGA X GAA AGCCAUCC  GGAUGCCCCUA AAA  3228 GGAUCCAG CUGAUGA X GAA AGCCAUCC  GGAUGGCCC CUGAUGA X GAA AGCCAUCC  GGAUGGCCC CUGAUGA X GAA AUCCAUCC  GAAAGAUC CUCACAC CUGAUGA X GAA AUCCAUCC  GAAACCAUCC UCCACACACACC  GGAUGCCCCUA AAACACACC  GGAUGCCCCUA AAACACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GGAUGCCCCCAACACC  GAAACCACCC  GAAACCACCC  GAAACCCACC  CUCCACACACC  GAAACCACC  CUCCACACACACC  GAAACCACC  CUCCACACACACC  GAAACCACC  CUCCACACACACC  GAAACCACC  CUCCACACACACC  CUCCACACACACC  CCCCGGGAUCC  CCCCGGGAUCC  ACCCCGGCACACC  CCCCGGGAUCC  ACCCCGGCACACC |     | 3114 | CUCAGAUA CUGAUGA X GAA AAGGAUGU | ACAUCCUUU UAUCUGAG |
| 3118 UGUUCUCA CUGAUGA X GAA AUAAAAGG CCUUUUAUC UGAGAGAUU UGAAGAUUU UGAAGAUAUU UGAAGAAAAAAAA  | 10  | 3115 | UCUCAGAU CUGAUGA X GAA AAAGGAUG | CAUCCUUUU AUCUGAGA |
| 3140 AAGUCGCA CUGAUGA X GAA AUCUUCAC GUGAAGAUU UG 3141 AAAGUCGC CUGAUGA X GAA AAUCUUCA UGAAGAUUU UG 3148 CCAGGCCA CUGAUGA X GAA AAUCUUCA UGAAGAUUU GG 3149 GCCAGGCC CUGAUGA X GAA AAGUCGCA UGCGACUUU GG 3165 CUUAUAAA CUGAUGA X GAA AUCCCGGG CCCGGGAUA UU 3167 UUCUUAUA CUGAUGA X GAA AUAUCCCC CGGGAUAUU UA 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3169 GGUUCUUA CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AAUAUCCC GGAUAUUU AU 3183 CCUCACAU CUGAUGA X GAA AUAAAUAU AUAUUUAUA AG 3184 UCCUCACA CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3201 AAGUCGAG CUGAUGA X GAA AUCAGGG CCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGAGAGAUA CUG 3209 UUUAGGGG CUGAUGA X GAA AGUAUCUC GAGAGAGAUA CUG 3210 UUUUAGGG CUGAUGA X GAA AGUAUCUC GAGAUACUC GAG 3228 GGAUUCAG CUGAUGA X GAA AGGCGAGG CUCCGACUU CCC 3228 GGAUUCAG CUGAUGA X GAA AGGCGAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGGCGAAG CUUCCCCUA AAA 3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3241 CCUUGUCA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3241 CCUUGUCA CUGAUGA X GAA AUGAGAUUC GAAUCCAUC UUCA 3241 CCUUGUCA CUGAUGA X GAA AUGAGAUUC GAAUCCAUC UUCA   |     | 3116 | UUCUCAGA CUGAUGA X GAA AAAAGGAU | AUCCUUUUA UCUGAGAA |
| 3141 AAAGUCGC CUGAUGA X GAA AAUCUUCA UGAAGAUUU GC 3149 GCCAGGCC CUGAUGA X GAA AGUCGCAA UUGCGACUUU GG 3165 CUUAUAAA CUGAUGA X GAA AAGUCGCA UGCGACUUU GG 3167 UUCUUAUA CUGAUGA X GAA AUAUCCCG CGGGAUAUU UA 3168 GUUCUUAU CUGAUGA X GAA AUAUCCC GGGAUAUUU AU 3169 GGUUCUUA CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AUAAAUAU AUAUUUAUA AG 3183 CCUCACAU CUGAUGA X GAA AUAAAUAU AUAUUUAUA AG 3184 UCCUCACA CUGAUGA X GAA AUCAGGGU ACCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AUCAGGG CCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUACUC GAC 3209 UUUAGGGG CUGAUGA X GAA AGUCUCCUC GAGGAGAUACC GAC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAG CUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAG CUCGACUU CCC 3215 AUCCAUUU CUGAUGA X GAA AGUCGAG CUCGACUUC CCC 3228 GGAUUCAG CUGAUGA X GAA AGGGGAAG CUCCGACUUC CCC 3228 GGAUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUGACUA AAA 3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUGACUUC CACAAAAAAAAAA  |     | 3118 | UGUUCUCA CUGAUGA X GAA AUAAAAGG | CCUUUUAUC UGAGAACA |
| 15 3148 CCAGGCCA CUGAUGA X GAA AGUCGCAA UUGCGACUU UG 3149 GCCAGGCC CUGAUGA X GAA AAGUCGCA UGCGACUUU GG 3165 CUUAUAAA CUGAUGA X GAA AUCCCGGG CCCGGGAUA UU 3167 UUCUUAUA CUGAUGA X GAA AUAUCCCG CGGGAUAUU UA 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3169 GGUUCUUA CUGAUGA X GAA AAAUAUCC GGAUAUUUA UA 3171 AGGGUUCU CUGAUGA X GAA AAAUAUCC GGAUAUUUA AG 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AAUCAGGG CCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AUCAGGG CCCUGAUUA UG 3201 AAGUCGAG CUGAUGA X GAA AGUCUCCUC GAGGAGAUA CUG 3209 UUUAGGGG CUGAUGA X GAA AGUCUCCU GAGAAUACUC GAC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3215 AUCCAUUU CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3228 GGAUUCAG CUGAUGA X GAA AGUCGAG CUCCACUUC CCC 3228 GGAUUCAG CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU  |     | 3140 | AAGUCGCA CUGAUGA X GAA AUCUUCAC | GUGAAGAUU UGCGACUU |
| 3149 GCCAGGCC CUGAUGA X GAA AAGUCGCAA UGCGACUU UGG 3165 CUUAUAAA CUGAUGA X GAA AUCCCGGG CCCGGGAUA UU 3167 UUCUUAUA CUGAUGA X GAA AUAUCCCG CGGGAUAUU UA 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3171 AGGGUUCU CUGAUGA X GAA AAAUAUCC GGAUAUUUA UA 3171 AGGGUUCU CUGAUGA X GAA AUAAAUAU AUAUUUAUA AG 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AAUCAGGG CCCUGAUUA UGG 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGAGAGAUA CUG 3201 GGGAAGUC CUGAUGA X GAA AGUCCCUC GAGAGACUC CUGAUGA X GAA AGUCCGAGU ACUCGACUU CCC 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3215 AUCCAUUU CUGAUGA X GAA AGUCGAGU CUCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGCGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3231 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGCCUC CUGAUGAAUC CAU  |     | 3141 |                                 | UGAAGAUUU GCGACUUU |
| 3165 CUUAUAAA CUGAUGA X GAA AUCCCGGG CCCGGGAUA UU 3167 UUCUUAUA CUGAUGA X GAA AUAUCCCC CGGGAUAUU UA 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3169 GGUUCUUA CUGAUGA X GAA AAUAUCCC GGAUAUUUA UA 3171 AGGGUUCU CUGAUGA X GAA AUAAAUAU AUAUUUUAUA AG 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AUCAGGG CCCUGAUUA UGI 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGAUACUC GAG 3209 UUUAGGGG CUGAUGA X GAA AGUAUCUC GAGAUACUC GAG 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU CUCGACUU CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU  | 15  |      |                                 | UUGCGACUU UGGCCUGG |
| 3167 UUCUUAUA CUGAUGA X GAA AUAUCCCG CGGGAUAUU UA 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AU 3169 GGUUCUUA CUGAUGA X GAA AAAUAUCC GGAUAUUUA UA 3171 AGGGUUCU CUGAUGA X GAA AUAAAUAU AUAUUUAUA AG 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AUCAGGG CCCUGAUUA UGG 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUG 3201 GGGAAGUC CUGAUGA X GAA AGUAUCUC GAGAUACUC GAG 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAG CUCGACUU CCC 3215 AUCCAUUU CUGAUGA X GAA AGGCGAAG CUCGACUUC CCC 3228 GGAUUCAG CUGAUGA X GAA AGGCGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3241 CCUUGUCA CUGAUGA X GAA AGGAUGGAU AUCCAUCUU UGA  |     |      |                                 | UGCGACUUU GGCCUGGC |
| 3168 GUUCUUAU CUGAUGA X GAA AAUAUCCC GGGAUAUUU AUA 3169 GGUUCUUA CUGAUGA X GAA AAAUAUCC GGAUAUUUA UAA 3171 AGGGUUCU CUGAUGA X GAA AUAAAUAU AUAUUUAUA AGA 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AUCAGGG CCCUGAUUA UGA 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUG 3201 GGGAAGUC CUGAUGA X GAA AGUCUCCUC GAGAUACUC GAG 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU CCCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA  |     |      |                                 | CCCGGGAUA UUUAUAAG |
| 3169 GGUUCUUA CUGAUGA X GAA AAAUAUCC GGAUAUUU AUA 3171 AGGGUUCU CUGAUGA X GAA AUAAAUAU AUAUUUAUA AG 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AUCAGGG CCCUGAUUA UGI 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUG 3209 UUUAGGGG CUGAUGA X GAA AGUAUCUC GAGAUACUC GAG 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCG 3210 UUUUAGGG CUGAUGA X GAA AGUCGAGU CUCGACUUC CCG 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3235 CAAAGAUG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGGAUGGAU AUCCAUCUU UGA   |     |      |                                 | CGGGAUAUU UAUAAGAA |
| 3171 AGGGUUCU CUGAUGA X GAA AAAUAUCC GGAUAUUUA UAX 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AAUCAGGG CCCUGAUUA UGI 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUG 3204 GGGAAGUC CUGAUGA X GAA AGUCUCCUC GAGGAGAUA CUG 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCG 3210 UUUUAGGG CUGAUGA X GAA AAGUCGAG CUCGACUUC CCG 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3235 CAAAGAUG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU  | 2.0 |      |                                 | GGGAUAUUU AUAAGAAC |
| 3183 CCUCACAU CUGAUGA X GAA AUCAGGGU ACCCUGAUU AUG 3184 UCCUCACA CUGAUGA X GAA AAUCAGGG CCCUGAUUA UGU 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUG 3201 GGGAAGUC CUGAUGA X GAA AGUAUCUC GAGAUACUC GAG 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AAGUCGAG CUCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA   | 20  |      |                                 | GGAUAUUUA UAAGAACC |
| 3184 UCCUCACA CUGAUGA X GAA AAUCAGGG CCCUGAUUA UGT 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUC 3204 GGGAAGUC CUGAUGA X GAA AGUAUCUC GAGAUACUC GAC 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AAGUCGAG CUCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUC 3235 CAAAGAUG CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA  |     |      |                                 | AUAUUUAUA AGAACCCU |
| 3201 AAGUCGAG CUGAUGA X GAA AUCUCCUC GAGGAGAUA CUC 25 3204 GGGAAGUC CUGAUGA X GAA AGUAUCUC GAGAUACUC GAC 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AAGUCGAG CUCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUC 3239 UUGUCAAA CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUC 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA  |     |      |                                 | ACCCUGAUU AUGUGAGG |
| 3204 GGGAAGUC CUGAUGA X GAA AGUAUCUC GAGAUACUC GAG 3209 UUUAGGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AAGUCGAG CUCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUC 3235 CAAAGAUG CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA  |     |      |                                 | CCCUGAUUA UGUGAGGA |
| 3219 UUUUAGGG CUGAUGA X GAA AGUCGAGU ACUCGACUU CCC 3210 UUUUAGGG CUGAUGA X GAA AAGUCGAG CUCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3235 CAAAGAUG CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA   | 25  |      |                                 | GAGGAGAUA CUCGACUU |
| 3210 UUUUAGGG CUGAUGA X GAA AAGUCGAG CUCGACUUC CCC 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 30 3235 CAAAGAUG CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA   | 25  |      |                                 | GAGAUACUC GACUUCCC |
| 3215 AUCCAUUU CUGAUGA X GAA AGGGGAAG CUCGACUUC CCC 3228 GGAUUCAG CUGAUGA X GAA AGGGGAAG CUUCCCCUA AAA 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 3239 UUGUCAAA CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA   |     |      |                                 | ACUCGACUU CCCCUAAA |
| 3228 GGAUUCAG CUGAUGA X GAA AGCCAUCC GGAUGGCUC CUG 30 3235 CAAAGAUG CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA   |     |      |                                 | CUCGACUUC CCCUAAAA |
| 30 3235 CAAAGAUG CUGAUGA X GAA AUUCAGGA UCCUGAAUC CAU 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA  |     |      |                                 | CUUCCCCUA AAAUGGAU |
| 3239 UUGUCAAA CUGAUGA X GAA AUGGAUUC GAAUCCAUC UUU 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA  | 30  |      |                                 | GGAUGGCUC CUGAAUCC |
| 3241 CCUUGUCA CUGAUGA X GAA AGAUGGAU AUCCAUCUU UGA   | 30  |      |                                 | UCCUGAAUC CAUCUUUG |
| 3242 30000000000000000000000000000000000   |     |      |                                 | GAAUCCAUC UUUGACAA |
| 3242 ACCUUGUC CUGAUGA X GAA AAGAUGGA UCCAUCUUU GAC   |     |      |                                 | AUCCAUCUU UGACAAGG |
|  |     | 3242 | ACCUUGUC CUGAUGA X GAA AAGAUGGA | UCCAUCUUU GACAAGGU |

|    | 3251 | GUGCUGUA CUGAUGA X GAA ACCUUGUC | GACAAGGUC UACAGCAC |
|----|------|---------------------------------|--------------------|
|    | 3253 | UGGUGCUG CUGAUGA X GAA AGACCUUG | CAAGGUCUA CAGCACCA |
|    | 3277 | CGCCAUAG CUGAUGA X GAA ACCACACA | UGUGUGGUC CUAUGGCG |
|    | 3280 | ACACGCCA CUGAUGA X GAA AGGACCAC | GUGGUCCUA UGGCGUGU |
| 5  | 3289 | CCCACAGC CUGAUGA X GAA ACACGCCA | UGGCGUGUU GCUGUGGG |
|    | 3302 | AAGGAGAA CUGAUGA X GAA AUCUCCCA | UGGGAGAUC UUCUCCUU |
|    | 3304 | CUAAGGAG CUGAUGA X GAA AGAUCUCC | GGAGAUCUU CUCCUUAG |
|    | 3305 | CCUAAGGA CUGAUGA X GAA AAGAUCUC | GAGAUCUUC UCCUUAGG |
|    | 3307 | CCCCUAAG CUGAUGA X GAA AGAAGAUC | GAUCUUCUC CUUAGGGG |
| 10 | 3310 | AACCCCCU CUGAUGA X GAA AGGAGAAG | CUUCUCCUU AGGGGGUU |
|    | 3311 | GAACCCCC CUGAUGA X GAA AAGGAGAA | UUCUCCUUA GGGGGUUC |
|    | 3318 | GUAUGGAG CUGAUGA X GAA ACCCCCUA | UAGGGGGUU CUCCAUAC |
|    | 3319 | GGUAUGGA CUGAUGA X GAA AACCCCCU | AGGGGGUUC UCCAUACC |
|    | 3321 | UGGGUAUG CUGAUGA X GAA AGAACCCC | GGGGUUCUC CAUACCCA |
| 15 | 3325 | CUCCUGGG CUGAUGA X GAA AUGGAGAA | UUCUCCAUA CCCAGGAG |
|    | 3352 | GGCUGCAG CUGAUGA X GAA AGUCUUCA | UGAAGACUU CUGCAGCC |
|    | 3353 | CGGCUGCA CUGAUGA X GAA AAGUCUUC | GAAGACUUC UGCAGCCG |
|    | 3397 | GUGUGGCA CUGAUGA X GAA ACUCCGGG | CCCGGAGUA UGCCACAC |
|    | 3413 | AUUUGGUA CUGAUGA X GAA AUUUCAGG | CCUGAAAUC UACCAAAU |
| 20 | 3415 | UGAUUUGG CUGAUGA X GAA AGAUUUCA | UGAAAUCUA CCAAAUCA |
|    | 3422 | UCCAACAU CUGAUGA X GAA AUUUGGUA |                    |
|    | 3427 | AGCAAUCC CUGAUGA X GAA ACAUGAUU | AAUCAUGUU GGAUUGCU |
|    | 3432 | GUGCCAGC CUGAUGA X GAA AUCCAACA | UGUUGGAUU GCUGGCAC |
|    | 3466 | GUUCAGCA CUGAUGA X GAA ACCGGGGC | GCCCCGGUU UGCUGAAC |
| 25 | 3467 | AGUUCAGC CUGAUGA X GAA AACCGGGG | CCCCGGUUU GCUGAACU |
|    | 3476 | UUCUCCAC CUGAUGA X GAA AGUUCAGC | GCUGAACUU GUGGAGAA |
|    | 3488 | AGGUCACC CUGAUGA X GAA AGUUUCUC | GAGAAACUU GGUGACCU |
|    | 3500 | UUGGCUUG CUGAUGA X GAA AGCAGGUC | GACCUGCUU CAAGCCAA |
|    | 3501 | GUUGGCUU CUGAUGA X GAA AAGCAGGU | ACCUGCUUC AAGCCAAC |
| 30 | 3512 | UCCUGUUG CUGAUGA X GAA ACGUUGGC | GCCAACGUC CAACAGGA |
|    | 3531 | GGGGAUGU CUGAUGA X GAA AUCUUUCC | GGAAAGAUU ACAUCCCC |
|    | 3532 | GGGGGAUG CUGAUGA X GAA AAUCUUUC | GAAAGAUUA CAUCCCCC |
|    | 3536 | UUGAGGGG CUGAUGA X GAA AUGUAAUC | GAUUACAUC CCCCUCAA |

|    | 3542 | AUGGCAUU CUGAUGA X GAA AGGGGGAU | AUCCCCCUC AAUGCCAU |
|----|------|---------------------------------|--------------------|
|    | 3551 | CUAGUCAG CUGAUGA X GAA AUGGCAUU | AAUGCCAUA CUGACUAG |
|    | 3558 | ACUGUUUC CUGAUGA X GAA AGUCAGUA | UACUGACUA GAAACAGU |
|    | 3567 | UGUGAAGC CUGAUGA X GAA ACUGUUUC | GAAACAGUA GCUUCACA |
| 5  | 3571 | AGUAUGUG CUGAUGA X GAA AGCUACUG | CAGUAGCUU CACAUACU |
|    | 3572 | GAGUAUGU CUGAUGA X GAA AAGCUACU | AGUAGCUUC ACAUACUC |
|    | 3577 | GGGUCGAG CUGAUGA X GAA AUGUGAAG | CUUCACAUA CUCGACCC |
|    | 3580 | UGGGGGUC CUGAUGA X GAA AGUAUGUG | CACAUACUC GACCCCCA |
|    | 3592 | CCUCAGAG CUGAUGA X GAA AGGUGGGG | CCCCACCUU CUCUGAGG |
| 10 | 3593 | uccucaga cugauga x gaa aagguggg | CCCACCUUC UCUGAGGA |
|    | 3595 | GGUCCUCA CUGAUGA X GAA AGAAGGUG | CACCUUCUC UGAGGACC |
|    | 3605 | UCCUUGAA CUGAUGA X GAA AGGUCCUC | GAGGACCUU UUCAAGGA |
|    | 3606 | GUCCUUGA CUGAUGA X GAA AAGGUCCU | AGGACCUUU UCAAGGAC |
|    | 3607 | CGUCCUUG CUGAUGA X GAA AAAGGUCC | GGACCUUUU CAAGGACG |
| 15 | 3608 | CCGUCCUU CUGAUGA X GAA AAAAGGUC | GACCUUUUC AAGGACGG |
|    | 3619 | GAUCUGCA CUGAUGA X GAA AGCCGUCC | GGACGGCUU UGCAGAUC |
|    | 3620 | GGAUCUGC CUGAUGA X GAA AAGCCGUC | GACGGCUUU GCAGAUCC |
|    | 3627 | AAAAUGUG CUGAUGA X GAA AUCUGCAA | UUGCAGAUC CACAUUUU |
|    | 3633 | GGAAUGAA CUGAUGA X GAA AUGUGGAU | AUCCACAUU UUCAUUCC |
| 20 | 3634 | CGGAAUGA CUGAUGA X GAA AAUGUGGA | UCCACAUUU UCAUUCCG |
|    | 3635 | CCGGAAUG CUGAUGA X GAA AAAUGUGG | CCACAUUUU CAUUCCGG |
|    | 3636 | UCCGGAAU CUGAUGA X GAA AAAAUGUG | CACAUUUUC AUUCCGGA |
|    | 3639 | GCUUCCGG CUGAUGA X GAA AUGAAAAU | AUUUUCAUU CCGGAAGC |
|    | 3640 | AGCUUCCG CUGAUGA X GAA AAUGAAAA | UUUUCAUUC CGGAAGCU |
| 25 | 3649 | CAUCAUCA CUGAUGA X GAA AGCUUCCG | CGGAAGCUC UGAUGAUG |
|    | 3664 | CGUUUACA CUGAUGA X GAA AUCUCACA | UGUGAGAUA UGUAAACG |
|    | 3668 | AAAGCGUU CUGAUGA X GAA ACAUAUCU | AGAUAUGUA AACGCUUU |
|    | 3675 | GAAUUUGA CUGAUGA X GAA AGCGUUUA | UAAACGCUU UCAAAUUC |
|    | 3676 | UGAAUUUG CUGAUGA X GAA AAGCGUUU | AAACGCUUU CAAAUUCA |
| 30 | 3677 | AUGAAUUU CUGAUGA X GAA AAAGCGUU | AACGCUUUC AAAUUCAU |
|    | 3682 | GGCUCAUG CUGAUGA X GAA AUUUGAAA | UUUCAAAUU CAUGAGCC |
|    | 3683 | AGGCUCAU CUGAUGA X GAA AAUUUGAA | UUCAAAUUC AUGAGCCU |
|    | 3701 | AAGGUUUU CUGAUGA X GAA AUUCUUUC | GAAAGAAUC AAAACCUU |
|    |      |                                 |                    |

PCT/US96/17480

|    | 3709 | GCUCCUCA CUGAUGA X GAA AGGUUUUG | CAAAACCUU UGAGGAGC |
|----|------|---------------------------------|--------------------|
|    | 3710 | AGCUCCUC CUGAUGA X GAA AAGGUUUU | AAAACCUUU GAGGAGCU |
|    | 3719 | UUCGGUGA CUGAUGA X GAA AGCUCCUC | GAGGAGCUU UCACCGAA |
|    | 3720 | GUUCGGUG CUGAUGA X GAA AAGCUCCU | AGGAGCUUU CACCGAAC |
| 5  | 3721 | AGUUCGGU CUGAUGA X GAA AAAGCUCC | GGAGCUUUC ACCGAACU |
|    | 3730 | UGGAGGUG CUGAUGA X GAA AGUUCGGU | ACCGAACUC CACCUCCA |
|    | 3736 | CAAACAUG CUGAUGA X GAA AGGUGGAG | CUCCACCUC CAUGUUUG |
|    | 3742 | AGUCCUCA CUGAUGA X GAA ACAUGGAG | CUCCAUGUU UGAGGACU |
|    | 3743 | UAGUCCUC CUGAUGA X GAA AACAUGGA | UCCAUGUUU GAGGACUA |
| 10 | 3751 | CCAGCUGA CUGAUGA X GAA AGUCCUCA | UGAGGACUA UCAGCUGG |
|    | 3753 | GUCCAGCU CUGAUGA X GAA AUAGUCCU | AGGACUAUC AGCUGGAC |
|    | 3765 | CAGAGUGC CUGAUGA X GAA AGUGUCCA | UGGACACUA GCACUCUG |
|    | 3771 | GCCCAGCA CUGAUGA X GAA AGUGCUAG | CUAGCACUC UGCUGGGC |
|    | 3781 | GCAAGGGG CUGAUGA X GAA AGCCCAGC | GCUGGGCUC CCCCUUGC |
| 15 | 3787 | GCUUCAGC CUGAUGA X GAA AGGGGGAG | CUCCCCCUU GCUGAAGC |
|    | 3799 | UCCAGGUG CUGAUGA X GAA ACCGCUUC | GAAGCGGUU CACCUGGA |
|    | 3800 | GUCCAGGU CUGAUGA X GAA AACCGCUU | AAGCGGUUC ACCUGGAC |
|    | 3829 | UCUUCAUG CUGAUGA X GAA AGGCCUUG | CAAGGCCUC CAUGAAGA |
| •  | 3839 | CUCAAGUC CUGAUGA X GAA AUCUUCAU | AUGAAGAUA GACUUGAG |
| 20 | 3844 | CUAUUCUC CUGAUGA X GAA AGUCUAUC | GAUAGACUU GAGAAUAG |
|    | 3851 | UUACUCGC CUGAUGA X GAA AUUCUCAA | UUGAGAAUA GCGAGUAA |
|    | 3858 | CUUGCUUU CUGAUGA X GAA ACUCGCUA | UAGCGAGUA AAAGCAAG |
|    | 3878 | AGAUCGGA CUGAUGA X GAA AGUCCCGC | GCGGGACUU UCCGAUCU |
|    | 3879 | CAGAUCGG CUGAUGA X GAA AAGUCCCG | CGGGACUUU CCGAUCUG |
| 25 | 3880 | GCAGAUCG CUGAUGA X GAA AAAGUCCC | GGGACUUUC CGAUCUGC |
|    | 3885 | CCUCGGCA CUGAUGA X GAA AUCGGAAA | UUUCCGAUC UGCCGAGG |
|    | 3901 | AGAAGCAG CUGAUGA X GAA AGCUGGGC | GCCCAGCUU CUGCUUCU |
|    | 3902 | GAGAAGCA CUGAUGA X GAA AAGCUGGG | CCCAGCUUC UGCUUCUC |
|    | 3907 | AGCUGGAG CUGAUGA X GAA AGCAGAAG | CUUCUGCUU CUCCAGCU |
| 30 | 3908 | CAGCUGGA CUGAUGA X GAA AAGCAGAA | UUCUGCUUC UCCAGCUG |
|    | 3910 | CACAGCUG CUGAUGA X GAA AGAAGCAG | CUGCUUCUC CAGCUGUG |
|    | 3926 | ACGGGCCU CUGAUGA X GAA AUGUGGCC | GGCCACAUC AGGCCCGU |
|    | 3949 | CCAGCUCA CUGAUGA X GAA AUUCAUCG | CGAUGAAUC UGAGCUGG |

|    | 3967 | AACAGCAG CUGAUGA X GAA ACUCCUUU | AAAGGAGUC CUGCUGUU |
|----|------|---------------------------------|--------------------|
|    | 3975 | GGGUGGAG CUGAUGA X GAA ACAGCAGG | CCUGCUGUU CUCCACCC |
|    | 3976 | GGGGUGGA CUGAUGA X GAA AACAGCAG | CUGCUGUUC UCCACCCC |
|    | 3978 | UGGGGGUG CUGAUGA X GAA AGAACAGC | GCUGUUCUC CACCCCCA |
| 5  | 3991 | CGGAGUUG CUGAUGA X GAA AGUCUGGG | CCCAGACUA CAACUCCG |
|    | 3997 | ACACCACG CUGAUGA X GAA AGUUGUAG | CUACAACUC CGUGGUGU |
|    | 4006 | AGGAGUAC CUGAUGA X GAA ACACCACG | CGUGGUGUU GUACUCCU |
|    | 4009 | GGGAGGAG CUGAUGA X GAA ACAACACC | GGUGUUGUA CUCCUCCC |
|    | 4012 | GCGGGGAG CUGAUGA X GAA AGUACAAC | GUUGUACUC CUCCCCGC |
| 10 | 4015 | CGGGCGGG CUGAUGA X GAA AGGAGUAC | GUACUCCUC CCCGCCCG |
|    | 4027 | AGAAGCUU CUGAUGA X GAA AGGCGGGC | GCCCGCCUA AAGCUUCU |
|    | 4033 | CUGGUGAG CUGAUGA X GAA AGCUUUAG | CUAAAGCUU CUCACCAG |
|    | 4034 | GCUGGUGA CUGAUGA X GAA AAGCUUUA | UAAAGCUUC UCACCAGC |
|    | 4036 | GGGCUGGU CUGAUGA X GAA AGAAGCUU | AAGCUUCUC ACCAGCCC |
| 15 | 4066 | AUGUAUAA CUGAUGA X GAA ACUGUCAG | CUGACAGUA UUAUACAU |
|    | 4068 | AGAUGUAU CUGAUGA X GAA AUACUGUC | GACAGUAUU AUACAUCU |
|    | 4069 | UAGAUGUA CUGAUGA X GAA AAUACUGU | ACAGUAUUA UACAUCUA |
|    | 4071 | CAUAGAUG CUGAUGA X GAA AUAAUACU | AGUAUUAUA CAUCUAUG |
|    | 4075 | AACUCAUA CUGAUGA X GAA AUGUAUAA | UUAUACAUC UAUGAGUU |
| 20 | 4077 | UAAACUCA CUGAUGA X GAA AGAUGUAU | AUACAUCUA UGAGUUUA |
|    | 4083 | UAGGUGUA CUGAUGA X GAA ACUCAUAG | CUAUGAGUU UACACCUA |
|    | 4084 | AUAGGUGU CUGAUGA X GAA AACUCAUA | UAUGAGUUU ACACCUAU |
|    | 4085 | AAUAGGUG CUGAUGA X GAA AAACUCAU | AUGAGUUUA CACCUAUU |
|    | 4091 | GAGCGGAA CUGAUGA X GAA AGGUGUAA | UUACACCUA UUCCGCUC |
| 25 | 4093 | UGGAGCGG CUGAUGA X GAA AUAGGUGU | ACACCUAUU CCGCUCCA |
|    | 4094 | GUGGAGCG CUGAUGA X GAA AAUAGGUG | CACCUAUUC CGCUCCAC |
|    | 4099 | CUCCUGUG CUGAUGA X GAA AGCGGAAU | AUUCCGCUC CACAGGAG |
|    | 4117 | GUCACGAA CUGAUGA X GAA AGCAGCUG | CAGCUGCUU UUCGUGAC |
|    | 4118 | GGUCACGA CUGAUGA X GAA AAGCAGCU | AGCUGCUUU UCGUGACC |
| 30 | 4119 | AGGUCACG CUGAUGA X GAA AAAGCAGC | GCUGCUUUU CGUGACCU |
|    | 4120 |                                 | CUGCUUUUC GUGACCUU |
|    |      | CACGAUUA CUGAUGA X GAA AGGUCACG | CGUGACCUU UAAUCGUG |
|    | 4129 | GCACGAUU CUGAUGA X GAA AAGGUCAC | GUGACCUUU AAUCGUGC |

|    | 4130 | AGCACGAU CUGAUGA X GAA AAAGGUCA | UGACCUUUA AUCGUGCU                                  |
|----|------|---------------------------------|---|
|    | 4133 | AAAAGCAC CUGAUGA X GAA AUUAAAGG | CCUUUAAUC GUGCUUUU                                  |
|    | 4139 | AAACAAAA CUGAUGA X GAA AGCACGAU | AUCGUGCUU UUUUGUUU                                  |
|    | 4140 | AAAACAAA CUGAUGA X GAA AAGCACGA | บดดบดดดบบบ บบบดบบบบ                                 |
| 5  | 4141 | AAAAACAA CUGAUGA X GAA AAAGCACG | cgugcuuuu นนguuuuu                                  |
|    | 4142 | AAAAAACA CUGAUGA X GAA AAAAGCAC | GUGCUUUUU UGUUUUUU                                  |
|    | 4143 | CAAAAAAC CUGAUGA X GAA AAAAAGCA | ugcuuuuuu guuuuuug                                  |
|    | 4146 | AAACAAAA CUGAUGA X GAA ACAAAAAA | עעעטעעע עעעטעעע                                     |
|    | 4147 | AAAACAAA CUGAUGA X GAA AACAAAAA | บบบบเดิกกา กการการการการการการการการการการการการการ |
| 10 | 4148 | CAAAACAA CUGAUGA X GAA AAACAAAA | บบบบฐบบบบ บบฐบบบบฐ                                  |
|    | 4149 | ACAAAACA CUGAUGA X GAA AAAACAAA | บบบเรียบบบบ บเรียบบบเรีย                            |
|    | 4150 | AACAAAAC CUGAUGA X GAA AAAAACAA | บบเรียบบบบบ เรียบบบเรียบ                            |
|    | 4153 | ACAAACAA CUGAUGA X GAA ACAAAAAA | บบบบบบเรนบ บบเรบบบเรบ                               |
|    | 4154 | AACAAACA CUGAUGA X GAA AACAAAAA | บบบบบเรียบบ บเรียบบเรียบ                            |
| 15 | 4155 | CAACAAAC CUGAUGA X GAA AAACAAAA | บบบบเรียบบบ เรียบบเรียบเร                           |
|    | 4158 | CAACAACA CUGAUGA X GAA ACAAAACA | UGUUUUGUU UGUUGUUG                                  |
|    | 4159 | GCAACAAC CUGAUGA X GAA AACAAAAC | GUUUUGUUU GUUGUUGC                                  |
|    | 4162 | ACAGCAAC CUGAUGA X GAA ACAAACAA | UUGUUUGUU GUUGCUGU                                  |
|    | 4165 | AAAACAGC CUGAUGA X GAA ACAACAAA | UUUGUUGUU GCUGUUUU                                  |
| 20 | 4171 | UUAGUCAA CUGAUGA X GAA ACAGCAAC | GUUGCUGUU UUGACUAA                                  |
|    | 4172 | GUUAGUCA CUGAUGA X GAA AACAGCAA | UUGCUGUUU UGACUAAC                                  |
|    | 4173 | UGUUAGUC CUGAUGA X GAA AAACAGCA | UGCUGUUUU GACUAACA                                  |
|    | 4178 | AUUCUUGU CUGAUGA X GAA AGUCAAAA | UUUUGACUA ACAAGAAU                                  |
|    | 4189 | ACUGGGGU CUGAUGA X GAA ACAUUCUU | AAGAAUGUA ACCCCAGU                                  |
| 25 | 4198 | ACGUCACU CUGAUGA X GAA ACUGGGGU | ACCCCAGUU AGUGACGU                                  |
|    | 4199 | CACGUCAC CUGAUGA X GAA AACUGGGG | CCCCAGUUA GUGACGUG                                  |
|    | 4216 | AACAAUAG CUGAUGA X GAA AUUCUUCA | UGAAGAAUA CUAUUGUU                                  |
|    | 4219 | UCUAACAA CUGAUGA X GAA AGUAUUCU | AGAAUACUA UUGUUAGA                                  |
|    | 4221 | UCUCUAAC CUGAUGA X GAA AUAGUAUU | AAUACUAUU GUUAGAGA                                  |
| 30 | 4224 | AUUUCUCU CUGAUGA X GAA ACAAUAGU | ACUAUUGUU AGAGAAAU                                  |
|    | 4225 | GAUUUCUC CUGAUGA X GAA AACAAUAG | CUAUUGUUA GAGAAAUC                                  |
|    | 4233 | GCGGGGG CUGAUGA X GAA AUUUCUCU  | AGAGAAAUC CCCCCGC                                   |
|    | 4249 | GUUACCCU CUGAUGA X GAA AGGCUUUG | CAAAGCCUC AGGGUAAC                                  |
|    |      |                                 |   |

PCT/US96/17480

|    | 4255 | GUCCAGGU | CUGAUGA | x | GAA | ACCCUGAG | CUCAGGGUA | ACCUGGAC |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 4282 | GGUCGCCA | CUGAUGA | x | GAA | AGGCACCU | AGGUGCCUC | UGGCGACC |
|    | 4323 | GCUGCAGG | CUGAUGA | x | GAA | AGGGUGGG | CCCACCCUC | CCUGCAGC |
|    | 4341 | ACUGCCUC | CUGAUGA | X | GAA | AGUCCCAC | GUGGGACUA | GAGGCAGU |
| 5  | 4350 | AAUGGGCU | CUGAUGA | x | GAA | ACUGCCUC | GAGGCAGUA | AGCCCAUU |
|    | 4358 | CAUGAGCU | CUGAUGA | X | GAA | AUGGGCUU | AAGCCCAUU | AGCUCAUG |
|    | 4359 | CCAUGAGC | CUGAUGA | X | GAA | AAUGGGCU | AGCCCAUUA | GCUCAUGG |
|    | 4363 | GCAGCCAU | CUGAUGA | X | GAA | AGCUAAUG | CAUUAGCUC | AUGGCUGC |
|    | 4387 | GAGAGACA | CUGAUGA | X | GAA | AGCAGGUC | GACCUGCUC | UGUCUCUC |
| 10 | 4391 | AUAAGAGA | CUGAUGA | X | GAA | ACAGAGCA | UGCUCUGUC | UCUCUUAU |
|    | 4393 | CCAUAAGA | CUGAUGA | X | GAA | AGACAGAG | CUCUGUCUC | UCUUAUGG |
|    | 4395 | CUCCAUAA | CUGAUGA | X | GAA | AGAGACAG | CUGUCUCUC | UUAUGGAG |
|    | 4397 | UCCUCCAU | CUGAUGA | X | GAA | AGAGAGAC | GUCUCUCUU | AUGGAGGA |
|    | 4398 | UUCCUCCA | CUGAUGA | X | GAA | AAGAGAGA | UCUCUCUUA | UGGAGGAA |
| 15 | 4445 | GCAUCCCA | CUGAUGA | X | GAA | AGCCUUUU | AAAAGGCUU | UGGGAUGC |
|    | 4446 | CGCAUCCC | CUGAUGA | X | GAA | AAGCCUUU | AAAGGCUUU | GGGAUGCG |
|    | 4456 | ACAGGACG | CUGAUGA | X | GAA | ACGCAUCC | GGAUGCGUC | CGUCCUGU |
|    | 4460 | CUCCACAG | CUGAUGA | X | GAA | ACGGACGC | GCGUCCGUC | CUGUGGAG |
|    | 4487 | GCAUAGCG | CUGAUGA | X | GAA | AGCCCCCU | AGGGGGCUC | CGCUAUGC |
| 20 | 4492 | AAGUGGCA | CUGAUGA | X | GAA | AGCGGAGC | GCUCCGCUA | UGCCACUU |
|    | 4500 | AGUCACUG | CUGAUGA | X | GAA | AGUGGCAU | AUGCCACUU | CAGUGACU |
|    | 4501 | AAGUCACU | CUGAUGA | X | GAA | AAGUGGCA | UGCCACUUC | AGUGACUU |
|    | 4509 | GGAGUGAG | CUGAUGA | X | GAA | AGUCACUG | CAGUGACUU | CUCACUCC |
|    | 4510 | AGGAGUGA | CUGAUGA | X | GAA | AAGUCACU | AGUGACUUC | UCACUCCU |
| 25 | 4512 | CCAGGAGU | CUGAUGA | X | GAA | AGAAGUCA | UGACUUCUC | ACUCCUGG |
|    | 4516 | GAGGCCAG | CUGAUGA | X | GAA | AGUGAGAA | UUCUCACUC | CUGGCCUC |
|    | 4524 | AAACAGCG | CUGAUGA | X | GAA | AGGCCAGG | CCUGGCCUC | CGCUGUUU |
|    | 4531 | GGGCCCGA | CUGAUGA | X | GAA | ACAGCGGA | UCCGCUGUU | UCGGGCCC |
|    | 4532 | GGGGCCCG | CUGAUGA | X | GAA | AACAGCGG | CCGCUGUUU | CGGGCCCC |
| 30 | 4533 | GGGGCCC  | CUGAUGA | X | GAA | AAACAGCG | CGCUGUUUC | GGCCCCC  |
|    | 4543 | CCUCUUGG | CUGAUGA | X | GAA | AGGGGGCC | GCCCCCUU  | CCAAGAGG |
|    | 4544 | ACCUCUUG | CUGAUGA | X | GAA | AAGGGGGC | GCCCCCUUC | CAAGAGGU |
|    | 4553 | UGCUCUGA | CUGAUGA | X | GAA | ACCUCUUG | CAAGAGGUA | UCAGAGCA |

|    | 4555 | UCUGCUCU CUGAUGA X GAA AUACCUCU | AGAGGUAUC AGAGCAGA |
|----|------|---------------------------------|--------------------|
|    | 4577 | GUCUAGGA CUGAUGA X GAA ACGUCCCU | AGGGACGUU UCCUAGAC |
|    | 4578 | GGUCUAGG CUGAUGA X GAA AACGUCCC | GGGACGUUU CCUAGACC |
|    | 4579 | UGGUCUAG CUGAUGA X GAA AAACGUCC | GGACGUUUC CUAGACCA |
| 5  | 4582 | CCCUGGUC CUGAUGA X GAA AGGAAACG | CGUUUCCUA GACCAGGG |
|    | 4598 | UUCCCGAG CUGAUGA X GAA ACAUGUGC | GCACAUGUU CUCGGGAA |
|    | 4599 | GUUCCCGA CUGAUGA X GAA AACAUGUG | CACAUGUUC UCGGGAAC |
|    | 4601 | UGGUUCCC CUGAUGA X GAA AGAACAUG | CAUGUUCUC GGGAACCA |
|    | 4614 | UUAAGAUU CUGAUGA X GAA ACUGUGGU | ACCACAGUU AAUCUUAA |
| 10 | 4615 | UUUAAGAU CUGAUGA X GAA AACUGUGG | CCACAGUUA AUCUUAAA |
|    | 4618 | AGAUUUAA CUGAUGA X GAA AUUAACUG | CAGUUAAUC UUAAAUCU |
|    | 4620 | AAAGAUUU CUGAUGA X GAA AGAUUAAC | GUUAAUCUU AAAUCUUU |
|    | 4621 | AAAAGAUU CUGAUGA X GAA AAGAUUAA | UUAAUCUUA AAUCUUUU |
|    | 4625 | CGGGAAAA CUGAUGA X GAA AUUUAAGA | UCUUAAAUC UUUUCCCG |
| 15 | 4627 | CCCGGGAA CUGAUGA X GAA AGAUUUAA | UUAAAUCUU UUCCCGGG |
|    | 4628 | UCCCGGGA CUGAUGA X GAA AAGAUUUA | UAAAUCUUU UCCCGGGA |
|    | 4629 | CUCCCGGG CUGAUGA X GAA AAAGAUUU | AAAUCUUUU CCCGGGAG |
|    | 4630 | ACUCCCGG CUGAUGA X GAA AAAAGAUU | AAUCUUUUC CCGGGAGU |
|    | 4639 | CAACAGAA CUGAUGA X GAA ACUCCCGG | CCGGGAGUC UUCUGUUG |
| 20 | 4641 | GACAACAG CUGAUGA X GAA AGACUCCC | GGGAGUCUU CUGUUGUC |
|    | 4642 | AGACAACA CUGAUGA X GAA AAGACUCC | GGAGUCUUC UGUUGUCU |
|    | 4646 | AAACAGAC CUGAUGA X GAA ACAGAAGA | ncancaean eacaeana |
|    | 4649 | GGUAAACA CUGAUGA X GAA ACAACAGA | UCUGUUGUC UGUUUACC |
|    | 4653 | GGAUGGUA CUGAUGA X GAA ACAGACAA | UUGUCUGUU UACCAUCC |
| 25 | 4654 | UGGAUGGU CUGAUGA X GAA AACAGACA | UGUCUGUUU ACCAUCCA |
|    | 4655 | UUGGAUGG CUGAUGA X GAA AAACAGAC | GUCUGUUUA CCAUCCAA |
|    | 4660 | AUGCUUUG CUGAUGA X GAA AUGGUAAA | UUUACCAUC CAAAGCAU |
|    | 4669 | AUGUUAAA CUGAUGA X GAA AUGCUUUG | CAAAGCAUA UUUAACAU |
|    | 4671 | ACAUGUUA CUGAUGA X GAA AUAUGCUU | AAGCAUAUU UAACAUGU |
| 30 | 4672 | CACAUGUU CUGAUGA X GAA AAUAUGCU | AGCAUAUUU AACAUGUG |
|    | 4673 | ACACAUGU CUGAUGA X GAA AAAUAUGC | GCAUAUUUA ACAUGUGU |
|    | 4682 | CCCCCACU CUGAUGA X GAA ACACAUGU | ACAUGUGUC AGUGGGGG |
|    | 4698 | CAGAAGCC CUGAUGA X GAA AGCGCCAC | GUGGCGCUU GGCUUCUG |

|    | 4703 | GGCCUCAG CUGAUG  | A :  | K GAZ | AGCCAAGC | GCUUGGCU  | J CUGAGGCC |
|----|------|------------------|------|-------|----------|-----------|------------|
|    | 4704 | UGGCCUCA CUGAUG  | ia 2 | K GAZ | AAGCCAAG | CUUGGCUU  | UGAGGCCA   |
|    | 4720 | GAACUGAU CUGAUG  | A    | K GAA | AUGGCUCU | AGAGCCAU  | AUCAGUUC   |
|    | 4723 | GAGGAACU CUGAUG  | A 2  | ( GAA | AUGAUGGC | GCCAUCAU  | AGUUCCUC   |
| 5  | 4727 | ACUAGAGG CUGAUG  | A J  | (GAA  | ACUGAUGA | UCAUCAGUI | J CCUCUAGU |
|    | 4728 | CACUAGAG CUGAUG  | A )  | GAA   | AACUGAUG | CAUCAGUUC | CUCUAGUG   |
|    | 4731 | UCUCACUA CUGAUG  | A )  | GAA   | AGGAACUG | CAGUUCCUC | UAGUGAGA   |
|    | 4733 | CAUCUCAC CUGAUG  | A )  | GAA   | AGAGGAAC | GUUCCUCUA | GUGAGAUG   |
|    | 4745 | AUGACCUC CUGAUG  | A X  | GAA   | AUGCAUCU | AGAUGCAUU | GAGGUCAU   |
| 10 | 4751 | UUGGGUAU CUGAUG  | A X  | GAA   | ACCUCAAU | AUUGAGGUO | AUACCCAA   |
|    | 4754 | AGCUUGGG CUGAUG  | A X  | GAA   | AUGACCUC | GAGGUCAUA | CCCAAGCU   |
|    | 4763 | AGGCCUGC CUGAUG. | АХ   | GAA   | AGCUUGGG | CCCAAGCUU | GCAGGCCU   |
|    | 4777 | AGUAUGCG CUGAUG  | A X  | GAA   | AGGUCAGG | CCUGACCUU | CGCAUACU   |
|    | 4778 | CAGUAUGC CUGAUG  | A X  | GAA   | AAGGUCAG | CUGACCUUC | GCAUACUG   |
| 15 | 4783 | GUGAGCAG CUGAUG  | A X  | GAA   | AUGCGAAG | CUUCGCAUA | CUGCUCAC   |
|    | 4789 | CUCCCCGU CUGAUG  | A X  | GAA   | AGCAGUAU | AUACUGCUC | ACGGGGAG   |
|    | 4799 | GACCACUU CUGAUG  | A X  | GAA   | ACUCCCCG | CGGGGAGUU | AAGUGGUC   |
|    | 4800 | GGACCACU CUGAUG  | A X  | GAA   | AACUCCCC | GGGGAGUUA | AGUGGUCC   |
|    | 4807 | CCAAACUG CUGAUG  | X A  | GAA   | ACCACUUA | UAAGUGGUC | CAGUUUGG   |
| 20 | 4812 | CUAGGCCA CUGAUGA | X A  | GAA   | ACUGGACC | GGUCCAGUU | UGGCCUAG   |
|    | 4813 | ACUAGGCC CUGAUGA | X    | GAA   | AACUGGAC | GUCCAGUUU | GGCCUAGU   |
|    | 4819 | AACCUUAC CUGAUGA | X    | GAA   | AGGCCAAA | UUUGGCCUA | GUAAGGUU   |
|    | 4822 | GGCAACCU CUGAUGA | X    | GAA   | ACUAGGCC | GGCCUAGUA | AGGUUGCC   |
|    | 4827 | CAGUAGGC CUGAUGA | X    | GAA   | ACCUUACU | AGUAAGGUU | GCCUACUG   |
| 25 | 4832 | CCCAUCAG CUGAUGA | X    | GAA   | AGGCAACC | GGUUGCCUA | CUGAUGGG   |
|    | 4843 | UGGCUUUU CUGAUGA | X    | GAA   | AGCCCAUC | GAUGGGCUC | AAAAGCCA   |
|    | 4855 | CUGUUUAA CUGAUGA | X    | GAA   | AUGUGGCU | AGCCACAUU | UUAAACAG   |
|    | 4856 | CCUGUUUA CUGAUGA | X    | GAA   | AAUGUGGC | GCCACAUUU | UAAACAGG   |
|    | 4857 | ACCUGUUU CUGAUGA | X    | GAA   | AAAUGUGG | CCACAUUUU | AAACAGGU   |
| 30 | 4858 | AACCUGUU CUGAUGA | Х    | GAA   | AAAAUGUG | CACAUUUUA | AACAGGUU   |
|    | 4866 | UGAGAUAA CUGAUGA | X    | GAA   | ACCUGUUU | AAACAGGUU | UUAUCUCA   |
|    | 4867 | UUGAGAUA CUGAUGA | X    | GAA   | AACCUGUU | AACAGGUUU | UAUCUCAA   |
|    | 4868 | CUUGAGAU CUGAUGA | X    | GAA   | AAACCUGU | ACAGGUUUU | AUCUCAAG   |
|    |      |                  |      |       |          |           |            |

PCT/US96/17480 WO 97/15662

|    | 4869 | ACUUGAGA CUGAUGA X GAA AAAACCUG | CAGGUUUUA UCUCAAGU |
|----|------|---------------------------------|--------------------|
|    | 4871 | AUACUUGA CUGAUGA X GAA AUAAAACC | GGUUUUAUC UCAAGUAU |
|    | 4873 | UAAUACUU CUGAUGA X GAA AGAUAAAA | UUUUAUCUC AAGUAUUA |
|    | 4878 | UAUAUUAA CUGAUGA X GAA ACUUGAGA | UCUCAAGUA UUAAUAUA |
| 5  | 4880 | UAUAUAUU CUGAUGA X GAA AUACUUGA | UCAAGUAUU AAUAUAUA |
|    | 4881 | CUAUAUAU CUGAUGA X GAA AAUACUUG | CAAGUAUUA AUAUAUAG |
|    | 4884 | UGUCUAUA CUGAUGA X GAA AUUAAUAC | GUAUUAAUA UAUAGACA |
|    | 4886 | CUUGUCUA CUGAUGA X GAA AUAUUAAU | AUUAAUAUA UAGACAAG |
|    | 4888 | GUCUUGUC CUGAUGA X GAA AUAUAUUA | UAAUAUAUA GACAAGAC |
| 10 | 4900 | UAAUGCAU CUGAUGA X GAA AGUGUCUU | AAGACACUU AUGCAUUA |
|    | 4901 | AUAAUGCA CUGAUGA X GAA AAGUGUCU | AGACACUUA UGCAUUAU |
|    | 4907 | AACAGGAU CUGAUGA X GAA AUGCAUAA | UUAUGCAUU AUCCUGUU |
|    | 4908 | AAACAGGA CUGAUGA X GAA AAUGCAUA | UAUGCAUUA UCCUGUUU |
|    | 4910 | UAAAACAG CUGAUGA X GAA AUAAUGCA | UGCAUUAUC CUGUUUUA |
| 15 | 4915 | AUAUAUAA CUGAUGA X GAA ACAGGAUA | UAUCCUGUU UUAUAUAU |
|    | 4916 | GAUAUAUA CUGAUGA X GAA AACAGGAU | AUCCUGUUU UAUAUAUC |
|    | 4917 | GGAUAUAU CUGAUGA X GAA AAACAGGA | UCCUGUUUU AUAUAUCC |
|    | 4918 | UGGAUAUA CUGAUGA X GAA AAAACAGG | CCUGUUUUA UAUAUCCA |
|    | 4920 | AUUGGAUA CUGAUGA X GAA AUAAAACA | UGUUUUAUA UAUCCAAU |
| 20 | 4922 | UCAUUGGA CUGAUGA X GAA AUAUAAAA | UUUUAUAUA UCCAAUGA |
|    | 4924 | AUUCAUUG CUGAUGA X GAA AUAUAUAA | UUAUAUAUC CAAUGAAU |
|    | 4933 | CCCAGUUA CUGAUGA X GAA AUUCAUUG | CAAUGAAUA UAACUGGG |
|    | 4935 | GCCCCAGU CUGAUGA X GAA AUAUUCAU | AUGAAUAUA ACUGGGGC |
|    | 4948 | UGACUCUU CUGAUGA X GAA ACUCGCCC | GGGCGAGUU AAGAGUCA |
| 25 | 4949 | AUGACUCU CUGAUGA X GAA AACUCGCC | GGCGAGUUA AGAGUCAU |
|    | 4955 | UAGACCAU CUGAUGA X GAA ACUCUUAA | UUAAGAGUC AUGGUCUA |
|    | 4961 | CUUUUCUA CUGAUGA X GAA ACCAUGAC | GUCAUGGUC UAGAAAAG |
|    | 4963 | CCCUUUUC CUGAUGA X GAA AGACCAUG | CAUGGUCUA GAAAAGGG |
|    | 4974 | UACAGAGA CUGAUGA X GAA ACCCCUUU | AAAGGGGUU UCUCUGUA |
| 30 | 4975 | GUACAGAG CUGAUGA X GAA AACCCCUU | AAGGGGUUU CUCUGUAC |
|    | 4976 | GGUACAGA CUGAUGA X GAA AAACCCCU | AGGGGUUUC UCUGUACC |
|    | 4978 | UGGGUACA CUGAUGA X GAA AGAAACCC | GGGUUUCUC UGUACCCA |
|    | 4982 | GAUUUGGG CUGAUGA X GAA ACAGAGAA | UUCUCUGUA CCCAAAUC |
|    |      |                                 |                    |

|    | 4990 | ACCAGCCC CUGAUGA X GAA AUUUGGGU  | ACCCAAAUC GGGCUGGU |
|----|------|----------------------------------|--------------------|
|    | 4999 |                                  | GGGCUGGUU GGACCAAG |
|    | 5029 |                                  | AGAGUGGUU GUCCCAGC |
|    | 5032 |                                  |                    |
| 5  | 5039 |                                  | GUGGUUGUC CCAGCUAU |
|    | 5041 |                                  | UCCCAGCUA UAGUUACU |
|    | 5044 |                                  | CCAGCUAUA GUUACUAA |
|    | 5045 |                                  | GCUAUAGUU ACUAAACU |
|    | 5048 | GAGUAGUU CUGAUGA X GAA AGUAACUA  | CUAUAGUUA CUAAACUA |
| 10 | 5053 | UGGGUGAG CUGAUGA X GAA AGUUUAGU  | UAGUUACUA AACUACUC |
|    | 5056 | CUUUGGGU CUGAUGA X GAA AGUAGUUU  | ACUAAACUA CUCACCCA |
|    | 5066 | GAGGUCCC CUGAUGA X GAA ACUUUGGG  | AAACUACUC ACCCAAAG |
|    | 5074 | AAGCCAGU CUGAUGA X GAA AGGUCCCA  | CCCAAAGUU GGGACCUC |
|    | 5082 | GUAAAGAG CUGAUGA X GAA AGCCAGUG  | UGGGACCUC ACUGGCUU |
| 15 | 5083 | AGUAAAGA CUGAUGA X GAA AAGCCAGU  | CACUGGCUU CUCUUUAC |
|    | 5085 | GAAGUAAA CUGAUGA X GAA AGAAGCCA  | ACUGGCUUC UCUUUACU |
|    | 5087 | AUGAAGUA CUGAUGA X GAA AGAGAAGC  | UGGCUUCUC UUUACUUC |
|    | 5088 | GAUGAAGU CUGAUGA X GAA AAGAGAAG  | GCUUCUCUU UACUUCAU |
|    | 5089 | UGAUGAAG CUGAUGA X GAA AAAGAGAA  | CUUCUCUUU ACUUCAUC |
| 20 | 5092 | CCAUGAUG CUGAUGA X GAA AGUAAAGA  | UUCUCUUUA CUUCAUCA |
|    | 5093 | UCCAUGAU CUGAUGA X GAA AAGUAAAG  | UCUUUACUU CAUCAUGG |
|    | 5096 | AAAUCCAU CUGAUGA X GAA AUGAAGUA  | CUUUACUUC AUCAUGGA |
|    | 5103 | GAUGGUGA CUGAUGA X GAA AUCCAUGA  | UACUUCAUC AUGGAUUU |
|    | 5104 | GGAUGGUG CUGAUGA X GAA AAUCCAUGA | UCAUGGAUU UCACCAUC |
| 25 | 5105 | GGGAUGGU CUGAUGA X GAA AAAUCCAU  | CAUGGAUUU CACCAUCC |
|    | 5111 |                                  | AUGGAUUUC ACCAUCCC |
|    | 5122 | UGCCUUGG CUGAUGA X GAA AUGGUGAA  | UUCACCAUC CCAAGGCA |
|    | 5134 | UCCUCUCA CUGAUGA X GAA ACUGCCUU  | AAGGCAGUC UGAGAGGA |
|    | 5141 | AUACUCUU CUGAUGA X GAA AGCUCCUC  | GAGGAGCUA AAGAGUAU |
| 30 | 5143 | UGGGCUGA CUGAUGA X GAA ACUCUUUA  | UAAAGAGUA UCAGCCCA |
|    | 5151 | UAUGGGCU CUGAUGA X GAA AUACUCUU  | AAGAGUAUC AGCCCAUA |
|    | 5151 | UUAAUAAA CUGAUGA X GAA AUGGGCUG  | CAGCCCAUA UUUAUUAA |
|    |      | GCUUAAUA CUGAUGA X GAA AUAUGGGC  | GCCCAUAUU UAUUAAGC |
|    | 5154 | UGCUUAAU CUGAUGA X GAA AAUAUGGG  | CCCAUAUUU AUUAAGCA |

|    | 5155         | GUGCUUAA | CUGAUGA | X          | GAA | AAAUAUGG  | CCAUAUUUA | UUAAGCAC   |
|----|--------------|----------|---------|------------|-----|-----------|-----------|------------|
|    | 5157         | AAGUGCUU | CUGAUGA | . x        | GAA | UAUAAAUAU | DUAUUUAUA | J AAGCACUU |
|    | 5158         | AAAGUGCU | CUGAUGA | . x        | GAA | AAUAAAUA  | UAUUUAUUA | AGCACUUU   |
|    | 5165         | GGAGCAUA | CUGAUGA | . <b>x</b> | GAA | AGUGCUUA  | UAAGCACUU | UAUGCUCC   |
| 5  | 5166         | AGGAGCAU | CUGAUGA | . <b>x</b> | GAA | AAGUGCUU  | AAGCACUUU | AUGCUCCU   |
|    | 5167         | AAGGAGCA | CUGAUGA | X          | GAA | AAAGUGCU  | AGCACUUUA | ugcuccuu   |
|    | 5172         | GUGCCAAG | CUGAUGA | x          | GAA | AGCAUAAA  | UUUAUGCUC | CUUGGCAC   |
|    | 5175         | GCUGUGCC | CUGAUGA | X          | GAA | AGGAGCAU  | AUGCUCCUU | GGCACAGC   |
|    | 5195         | GCAUAAAU | CUGAUGA | x          | GAA | ACACAUCA  | UGAUGUGUA | AUUUAUGC   |
| 10 | 5198         | CUUGCAUA | CUGAUGA | X          | GAA | AUUACACA  | UGUGUAAUU | UAUGCAAG   |
|    | 5199         | GCUUGCAU | CUGAUGA | x          | GAA | AAUUACAC  | GUGUAAUUU | AUGCAAGC   |
|    | 5200         | AGCUUGCA | CUGAUGA | x          | GAA | AAAUUACA  | UGUAAUUUA | UGCAAGCU   |
|    | 5209         | UGGAGAGG | CUGAUGA | x          | GAA | AGCUUGCA  | UGCAAGCUC | CCUCUCCA   |
|    | 5213         | UAGCUGGA | CUGAUGA | x          | GAA | AGGGAGCU  | AGCUCCCUC | UCCAGCUA   |
| 15 | 5215         | CCUAGCUG | CUGAUGA | x          | GAA | AGAGGGAG  | cucccucuc | CAGCUAGG   |
|    | 5221         | CUGAGUCC | CUGAUGA | x          | GAA | AGCUGGAG  | CUCCAGCUA | GGACUCAG   |
|    | 5227         | AAUAUCCU | CUGAUGA | x          | GAA | AGUCCUAG  | CUAGGACUC | AGGAUAUU   |
|    | <b>523</b> 3 | UUGACUAA | CUGAUGA | x          | GAA | AUCCUGAG  | CUCAGGAUA | UUAGUCAA   |
|    | 5235         | CAUUGACU | CUGAUGA | x          | GAA | AUAUCCUG  | CAGGAUAUU | AGUCAAUG   |
| 20 | 5236         | UCAUUGAC | CUGAUGA | x          | GAA | AAUAUCCU  | AGGAUAUUA | GUCAAUGA   |
|    | 5239         | GGCUCAUU | CUGAUGA | X          | GAA | ACUAAUAU  | AUAUUAGUC | AAUGAGCC   |
|    | 5250         | υυςςυυυυ | CUGAUGA | X          | GAA | AUGGCUCA  | UGAGCCAUC | AAAAGGAA   |
|    | 5273         | AAAUAAGA | CUGAUGA | X          | GAA | AGGUUUUU  | AAAAACCUA | UCUUAUUU   |
|    | 5275         | GAAAAUAA | CUGAUGA | X          | GAA | AUAGGUUU  | AAACCUAUC | UUAUUUUC   |
| 25 | 5277         | AUGAAAAU | CUGAUGA | X          | GAA | AGAUAGGU  | ACCUAUCUU | AUUUUCAU   |
|    | 5278         | GAUGAAAA | CUGAUGA | x          | GAA | AAGAUAGG  | CCUAUCUUA | UUUUCAUC   |
|    | 5280         | CAGAUGAA | CUGAUGA | X          | GAA | AUAAGAUA  | UAUCUUAUU | UUCAUCUG   |
|    | 5281         | ACAGAUGA | CUGAUGA | x          | GAA | AAUAAGAU  | AUCUUAUUU | UCAUCUGU   |
|    | 5282         | AACAGAUG | CUGAUGA | x          | GAA | AAAUAAGA  | UCUUAUUUU | CAUCUGUU   |
| 30 | 5283         | AAACAGAU | CUGAUGA | x          | GAA | AAAAUAAG  | CUUAUUUUC | AUCUGUUU   |
|    | 5286         | AUGAAACA | CUGAUGA | x          | GAA | AUGAAAAU  | AUUUUCAUC | UGUUUCAU   |
|    | 5290         | AGGUAUGA | CUGAUGA | x          | GAA | ACAGAUGA  | UCAUCUGUU | UCAUACCU   |
|    | 5291         | AAGGUAUG | CUGAUGA | x          | GAA | AACAGAUG  | CAUCUGUUU | CAUACCUU   |
|    |              |          |         |            |     |           |           |            |

|    | 5292 | CAAGGUAU CUGAUGA X GAA AAACAGAU | AUCUGUUUC AUACCUUG |
|----|------|---------------------------------|--------------------|
|    | 5295 | AGACAAGG CUGAUGA X GAA AUGAAACA |                    |
|    | 5299 | CCCCAGAC CUGAUGA X GAA AGGUAUGA | UCAUACCUU GUCUGGGG |
|    | 5302 | AGACCCCA CUGAUGA X GAA ACAAGGUA | UACCUUGUC UGGGGUCU |
| 5  | 5309 | CGUCAUUA CUGAUGA X GAA ACCCCAGA | UCUGGGGUC UAAUGACG |
|    | 5311 | AUCGUCAU CUGAUGA X GAA AGACCCCA | UGGGGUCUA AUGACGAU |
|    | 5331 | CCCAUGUC CUGAUGA X GAA ACCCUGUU | AACAGGGUA GACAUGGG |
|    | 5350 | CCCUUUUC CUGAUGA X GAA ACCCUGUC | GACAGGGUA GAAAAGGG |
|    | 5367 | ACCCCAAA CUGAUGA X GAA AGCGGGCA | UGCCCGCUC UUUGGGGU |
| 10 | 5369 | AGACCCCA CUGAUGA X GAA AGAGCGGG | CCCGCUCUU UGGGGUCU |
|    | 5370 | UAGACCCC CUGAUGA X GAA AAGAGCGG | CCGCUCUUU GGGGUCUA |
|    | 5376 | CAUCUCUA CUGAUGA X GAA ACCCCAAA | UUUGGGGUC UAGAGAUG |
|    | 5378 | CUCAUCUC CUGAUGA X GAA AGACCCCA | UGGGGUCUA GAGAUGAG |
|    | 5395 | AUUUUAGA CUGAUGA X GAA ACCCAGGG | CCCUGGGUC UCUAAAAU |
| 15 | 5397 | CCAUUUUA CUGAUGA X GAA AGACCCAG | CUGGGUCUC UAAAAUGG |
|    | 5399 | AGCCAUUU CUGAUGA X GAA AGAGACCC | GGGUCUCUA AAAUGGCU |
|    | 5408 | UUCUAAGA CUGAUGA X GAA AGCCAUUU | AAAUGGCUC UCUUAGAA |
|    | 5410 | ACUUCUAA CUGAUGA X GAA AGAGCCAU | AUGGCUCUC UUAGAAGU |
|    | 5412 | CAACUUCU CUGAUGA X GAA AGAGAGCC | GGCUCUCUU AGAAGUUG |
| 20 | 5413 | ACAACUUC CUGAUGA X GAA AAGAGAGC | GCUCUCUUA GAAGUUGU |
|    | 5419 | GCACAUAC CUGAUGA X GAA ACUUCUAA | UUAGAAGUU GUAUGUGC |
|    | 5422 | UUUGCACA CUGAUGA X GAA ACAACUUC | GAAGUUGUA UGUGCAAA |
|    | 5432 | CAGACCAU CUGAUGA X GAA AUUUGCAC | GUGCAAAUU AUGGUCUG |
|    | 5433 | ACAGACCA CUGAUGA X GAA AAUUUGCA | UGCAAAUUA UGGUCUGU |
| 25 | 5438 | AGCACACA CUGAUGA X GAA ACCAUAAU | AUUAUGGUC UGUGUGCU |
|    | 5447 | CACGACCU CUGAUGA X GAA AGCACACA | UGUGUGCUU AGGUCGUG |
|    | 5448 | GCACGACC CUGAUGA X GAA AAGCACAC | GUGUGCUUA GGUCGUGC |
|    | 5452 | GUGUGCAC CUGAUGA X GAA ACCUAAGC | GCUUAGGUC GUGCACAC |
|    | 5475 | CCAGCUGU CUGAUGA X GAA ACCGGCUC | GAGCCGGUC ACAGCUGG |
| 30 | 5497 | AAAGCAGC CUGAUGA X GAA AUUCAUCG | CGAUGAAUA GCUGCUUU |
|    | 5504 | CUCUCCCA CUGAUGA X GAA AGCAGCUA | UAGCUGCUU UGGGAGAG |
|    | 5505 | GCUCUCCC CUGAUGA X GAA AAGCAGCU | AGCUGCUUU GGGAGAGC |
|    | 5524 | UAAGUGGC CUGAUGA X GAA AGCAUGCU | AGCAUGCUA GCCACUUA |

|    | 5531 | AGAGAAUU | CUGAUGA | X | GAA | AGUGGCUA | UAGCCACUU | AAUUCUCU |
|----|------|----------|---------|---|-----|----------|-----------|----------|
|    | 5532 | CAGAGAAU | CUGAUGA | X | GAA | AAGUGGCU | AGCCACUUA | AUUCUCUG |
|    | 5535 | GGUCAGAG | CUGAUGA | X | GAA | AUUAAGUG | CACUUAAUU | CUCUGACC |
|    | 5536 | CGGUCAGA | CUGAUGA | X | GAA | AAUUAAGU | ACUUAAUUC | UCUGACCG |
| 5  | 5538 | CCCGGUCA | CUGAUGA | X | GAA | AGAAUUAA | UUAAUUCUC | UGACCGGG |
|    | 5554 | GUACCCAU | CUGAUGA | X | GAA | AUGCUGGC | GCCAGCAUC | AUGGGUAC |
|    | 5561 | GGAGCAGG | CUGAUGA | X | GAA | ACCCAUGA | UCAUGGGUA | CCUGCUCC |
|    | 5568 | ACACAGGG | CUGAUGA | X | GAA | AGCAGGUA | UACCUGCUC | cccugugu |
|    | 5577 | GGAUGGGG | CUGAUGA | X | GAA | ACACAGGG | CCCUGUGUA | CCCCAUCC |
| 10 | 5584 | ACCUUAAG | CUGAUGA | X | GAA | AUGGGGUA | UACCCCAUC | CUUAAGGU |
|    | 5587 | AAAACCUU | CUGAUGA | X | GAA | AGGAUGGG | CCCAUCCUU | AAGGUUUU |
|    | 5588 | GAAAACCU | CUGAUGA | x | GAA | AAGGAUGG | CCAUCCUUA | AGGUUUUC |
|    | 5593 | AGACAGAA | CUGAUGA | X | GAA | ACCUUAAG | CUUAAGGUU | UUCUGUCU |
|    | 5594 | CAGACAGA | CUGAUGA | X | GAA | AACCUUAA | UUAAGGUUU | ucugucug |
| 15 | 5595 | UCAGACAG | CUGAUGA | x | GAA | AAACCUUA | UAAGGUUUU | CUGUCUGA |
|    | 5596 | AUCAGACA | CUGAUGA | X | GAA | AAAACCUU | AAGGUUUUC | UGUCUGAU |
|    | 5600 | UCUCAUCA | CUGAUGA | X | GAA | ACAGAAAA | UUUUCUGUC | UGAUGAGA |
|    | 5627 | UCAGUGGG | CUGAUGA | X | GAA | AUUGCACU | AGUGCAAUC | CCCACUGA |
|    | 5660 | UGCACCAA | CUGAUGA | X | GAA | AGCCACAG | CUGUGGCUC | UUGGUGCA |
| 20 | 5662 | AGUGCACC | CUGAUGA | X | GAA | AGAGCCAC | GUGGCUCUU | GGUGCACU |
| _  | 5671 | UGGCUGGU | CUGAUGA | X | GAA | AGUGCACC | GGUGCACUC | ACCAGCCA |
|    | 5685 | UACUUGUC | CUGAUGA | X | GAA | AGUCCUGG | CCAGGACUA | GACAAGUA |
|    | 5693 | cccuuucc | CUGAUGA | X | GAA | ACUUGUCU | AGACAAGUA | GGAAAGGG |
|    | 5704 | GUGGCUAG | CUGAUGA | X | GAA | AGCCCUUU | AAAGGGCUU | CUAGCCAC |
| 25 | 5705 | UGUGGCUA | CUGAUGA | x | GAA | AAGCCCUU | AAGGGCUUC | UAGCCACA |
|    | 5707 | AGUGUGGC | CUGAUGA | X | GAA | AGAAGCCC | GGGCUUCUA | GCCACACU |
|    | 5731 | CCCUACCU | CUGAUGA | X | GAA | AUUUUCUU | AAGAAAAUC | AGGUAGGG |
|    | 5736 | GCCAGCCC | CUGAUGA | X | GAA | ACCUGAUU | AAUCAGGUA | GGGCUGGC |
|    | 5754 | UGGACAAA | CUGAUGA | X | GAA | AUGUCUUU | AAAGACAUC | UUUGUCCA |
| 30 | 5756 | AAUGGACA | CUGAUGA | x | GAA | AGAUGUCU | AGACAUCUU | UGUCCAUU |
|    | 5757 | GAAUGGAC | CUGAUGA | X | GAA | AAGAUGUC | GACAUCUUU | GUCCAUUC |
|    | 5760 | UGCGAAUG | CUGAUGA | X | GAA | ACAAAGAU | AUCUUUGUC | CAUUCGCA |
|    | 5764 | CUUUUGCG | CUGAUGA | X | GAA | AUGGACAA | UUGUCCAUU | CGCAAAAG |
|    |      |          |         |   |     |          |           |          |

|    | 5765         | GCUUUUGC CUGAUGA X (  | GAA AAUGGACA | UGUCCAUUC GCAAAAGC |
|----|--------------|-----------------------|--------------|--------------------|
|    | 5775         | GCCGACAA CUGAUGA X (  | GAA AGCUUUUG | CAAAAGCUC UUGUCGGC |
|    | 5777         | CAGCCGAC CUGAUGA X (  | SAA AGAGCUUU | AAAGCUCUU GUCGGCUG |
|    | 5780         | CUGCAGCC CUGAUGA X (  | AA ACAAGAGC  | GCUCUUGUC GGCUGCAG |
| 5  | 5794         | GCCUGACU CUGAUGA X C  | AA ACACACUG  | CAGUGUGUA AGUCAGGC |
|    | 5798         | CAUCGCCU CUGAUGA X C  | AA ACUUACAC  | GUGUAAGUC AGGCGAUG |
|    | 5818         | UUCUCUGG CUGAUGA X G  | AA AGCCUCUG  | CAGAGGCUA CCAGAGAA |
|    | 5852         | GGAUGAGA CUGAUGA X G  | AA ACCUCAGG  | CCUGAGGUU UCUCAUCC |
|    | 5853         | UGGAUGAG CUGAUGA X G  | AA AACCUCAG  | CUGAGGUUU CUCAUCCA |
| 10 | 5854         | CUGGAUGA CUGAUGA X G  | AA AAACCUCA  | UGAGGUUUC UCAUCCAG |
|    | 5856         | AUCUGGAU CUGAUGA X G  | AA AGAAACCU  | AGGUUUCUC AUCCAGAU |
|    | 5859         | GAUAUCUG CUGAUGA X G  | AA AUGAGAAA  | UUUCUCAUC CAGAUAUC |
|    | <b>586</b> 5 | UUGCUGGA CUGAUGA X G  | AA AUCUGGAU  | AUCCAGAUA UCCAGCAA |
|    | 5867         | AAUUGCUG CUGAUGA X G  | AA AUAUCUGG  | CCAGAUAUC CAGCAAUU |
| 15 | <b>587</b> 5 | CACCCCCC CUGAUGA X G  | AA AUUGCUGG  | CCAGCAAUU GGGGGGUG |
|    | 5896         | GGACCAUC CUGAUGA X G. | AA AUGGUCUU  | AAGACCAUA GAUGGUCC |
|    | 5903         | UAAUACAG CUGAUGA X G. | AA ACCAUCUA  | UAGAUGGUC CUGUAUUA |
|    | 5908         | CGGAAUAA CUGAUGA X G. | AA ACAGGACC  | GGUCCUGUA UUAUUCCG |
|    | 5910         | AUCGGAAU CUGAUGA X G  | AA AUACAGGA  | UCCUGUAUU AUUCCGAU |
| 20 | 5911         | AAUCGGAA CUGAUGA X G  | AA AAUACAGG  | CCUGUAUUA UUCCGAUU |
|    | 5913         | AAAAUCGG CUGAUGA X G  | AA AUAAUACA  | UGUAUUAUU CCGAUUUU |
|    | 5914         | UAAAAUCG CUGAUGA X G  | AA AAUAAUAC  | GUAUUAUUC CGAUUUUA |
|    | 5919         | AUUAUUAA CUGAUGA X GI | AA AUCGGAAU  | AUUCCGAUU UUAAUAAU |
|    | 5920         | GAUUAUUA CUGAUGA X GI | A AAUCGGAA   | UUCCGAUUU UAAUAAUC |
| 25 | 5921         | AGAUUAUU CUGAUGA X GA | A AAAUCGGA   | UCCGAUUUU AAUAAUCU |
|    | 5922         | UAGAUUAU CUGAUGA X GA | AAAAUCGG     | CCGAUUUUA AUAAUCUA |
|    | 5925         | AAUUAGAU CUGAUGA X GA | UAAAAUUA     | AUUUUAAUA AUCUAAUU |
|    | 5928         | ACGAAUUA CUGAUGA X GA | AAUUAUUAA    | UUAAUAAUC UAAUUCGU |
|    | 5930         | UCACGAAU CUGAUGA X GA | A AGAUUAUU   | AAUAAUCUA AUUCGUGA |
| 30 | 5933         | UGAUCACG CUGAUGA X GA | A AUUAGAUU   | AAUCUAAUU CGUGAUCA |
|    | 5934         | AUGAUCAC CUGAUGA X GA | A AAUUAGAU   | AUCUAAUUC GUGAUCAU |
|    | 5940         | CUCUUAAU CUGAUGA X GA | A AUCACGAA   | UUCGUGAUC AUUAAGAG |
|    | 5943         | AGUCUCUU CUGAUGA X GA | A AUGAUCAC   | GUGAUCAUU AAGAGACU |
|    |              |                       |              |                    |

PCT/US96/17480

WO 97/15662

183

|    | 5944          | AAGUCUCU | CUGAUGA | x | GAA | AAUGAUCA | UGAUCAUUA   | AGAGACUU |
|----|---------------|----------|---------|---|-----|----------|-------------|----------|
|    | 5 <b>9</b> 52 | AUUUACUA | CUGAUGA | X | GAA | AGUCUCUU | AAGAGACUU   | UAGUAAAU |
|    | 5953          | CAUUUACU | CUGAUGA | x | GAA | AAGUCUCU | AGAGACUUU   | AGUAAAUG |
|    | 5954          | ACAUUUAC | CUGAUGA | X | GAA | AAAGUCUC | GAGACUUUA   | GUAAAUGU |
| 5  | 5957          | GGGACAUU | CUGAUGA | X | GAA | ACUAAAGU | ACUUUAGUA   | AAUGUCCC |
|    | 5963          | GGAAAAGG | CUGAUGA | X | GAA | ACAUUUAC | GUAAAUGUC   | ccuuuucc |
|    | 5967          | UGUGGGAA | CUGAUGA | x | GAA | AGGGACAU | AUGUCCCUU   | UUCCCACA |
|    | 5968          | UUGUGGGA | CUGAUGA | x | GAA | AAGGGACA | UGUCCCUUU   | UCCCACAA |
|    | 5969          | UUUGUGGG | CUGAUGA | x | GAA | AAAGGGAC | GUCCCUUUU   | CCCACAAA |
| 10 | 5970          | UUUUGUGG | CUGAUGA | X | GAA | AAAAGGGA | υσοσυσσισ   | CCACAAAA |
|    | 5981          | CUUUUCUU | CUGAUGA | X | GAA | ACUUUUGU | ACAAAAGUA   | AAGAAAAG |
|    | 5992          | AAUCCCGA | CUGAUGA | x | GAA | AGCUUUUC | GAAAAGCUA   | UCGGGAUU |
|    | 5994          | AGAAUCCC | CUGAUGA | x | GAA | AUAGCUUU | AAAGCUAUC   | GGGAUUCU |
|    | 6000          | AACCAGAG | CUGAUGA | x | GAA | AUCCCGAU | AUCGGGAUU   | CUCUGGUU |
| 15 | 6001          | GAACCAGA | CUGAUGA | x | GAA | AAUCCCGA | UCGGGAUUC   | UCUGGUUC |
|    | 6003          | CAGAACCA | CUGAUGA | x | GAA | AGAAUCCC | GGGAUUCUC   | UGGUUCUG |
|    | 6008          | UUAAGCAG | CUGAUGA | x | GAA | ACCAGAGA | UCUCUGGUU   | CUGCUUAA |
|    | 6009          | UUUAAGCA | CUGAUGA | x | GAA | AACCAGAG | CUCUGGUUC   | UGCUUAAA |
|    | 6014          | AAGUCUUU | CUGAUGA | x | GAA | AGCAGAAC | GUUCUGCUU   | AAAGACUU |
| 20 | 6015          | UAAGUCUU | CUGAUGA | x | GAA | AAGCAGAA | UUCUGCUUA   | AAGACUUA |
|    | 6022          | CCAAAGCU | CUGAUGA | x | GAA | AGUCUUUA | UAAAGACUU . | AGCUUUGG |
|    | 6023          | UCCAAAGC | CUGAUGA | x | GAA | AAGUCUUU | AAAGACUUA   | GCUUUGGA |
|    | 6027          | AGGCUCCA | CUGAUGA | x | GAA | AGCUAAGU | ACUUAGCUU   | UGGAGCCU |
|    | 6028          | UAGGCUCC | CUGAUGA | x | GAA | AAGCUAAG | CUUAGCUUU   | GGAGCCUA |
| 25 | 6036          | AACUUUCA | CUGAUGA | X | GAA | AGGCUCCA | UGGAGCCUA   | UGAAAGUU |
|    | 6044          | GGCUGAUC | CUGAUGA | x | GAA | ACUUUCAU | AUGAAAGUU   | GAUCAGCC |

Where "X" represents stem II region of a HH ribozyme (Hertel et al., 1992 Nucleic Acids Res. 20 3252). The length of stem II may be  $\geq$  2 base-pairs.

184

Table IX: Mouse flt1 VEGF Receptor-Hairpin Ribozyme and Substrate Sequence

| Substrate            | AUGGUCA HOS KOUGG   | GUCAGCII GCII GGGACACC                                    | CACCGCG GIIC IIIGCCIIIIA                                  | ACGCGCII GCII CGCCICIC                                   | GGIIGIICII GCII IICIICA CAG                               | כישושה פנס מכטכאראפ                                      | מפשעפטש מעט מרטניטים                                     | GRIICHGI GCG GAGGAGG                                      | GGGNICG GCC CACGACCG                                      | Garage GCL OGUGGGAG  | AUGCCCII GCC CCGIIGEGG                                    | וואררררון מאון ממממארם                                    | INCERCIO GAU GGGCAAAG                                     | ACITATION OF CONTINUES                                    | AUCGGCA GAC CAAUACAA                                      |
|----------------------|---|---|---|--|---|--|--|---|---|--|---|---|---|---|---|
| НР Ribozyme Sequence | GUCCCAGC AGAA GACCAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGUGUCCC AGAA GCUGAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UAAGGCAA AGAA GCGGUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GACACCCG AGAA GCGCGU ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA | CUGUGAGA AGAA GACACC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAMAGAGA AGAA GGCCUG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA | CAUGAGUG AGAA GCCUCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGIA | CGGUCGUG AGAA GAGACC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CUCCCACA AGAA GAUGGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGIA | GGAUGAUG AGAA GUCUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGIIA | CGUCACCC AGAA GGGGAU ACCAGAGAAACACACGUUGUGGUACAUVACCUGGUA | CUUUGCCC AGAA GGGGUA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CGCAGUUC AGAA GUCCUA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGIA | GCCGAUGG AGAA GAUAGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UUGUAUUG AGAA GCCGAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA |
|                      | AGAA G  | AGAA GO   | AGAA GC   | AGAA GC  | AGAA GA   | AGAA GG  | GAA GC   | GAA GA  | GAA GA  | GAA GU   | GAA GG  | GAA GG  | GAA GU  | gaa gai   | GAA GCC   |
|                      | GUCCCAGC  | GGUGUCCC  | UAAGGCAA ,  | GACACCCG ,   | CUGUGAGA  | GANAGAGA 1   | CAUGAGUG A   | ceencene 1  | CUCCCACA A  | GGAUGAUG A   | CGUCACCC A  | CUUUGCCC A  | CGCAGUUC A  | GCCGAUGG A  | UUGUAUUG A  |
| nt.<br>Posi-<br>tion | 33  | 36  | 20  | 29   | 79  | 166  | 197  | 214   | 266   | 487  | 501   | 995   | 640   | 169   | 703   |
|                      | Ŋ   |   |   |  |   | 10   |  |   |   |  | 15  |   |   |   |   |

| opp.                  | ncc                  |   | GGA  | AAG  | ACA  | AGG  | ၁ဗဗ္ဗ  |  | 185<br>NAAG                                      | יממת   | AAA  | GCA.   | GAC  | GAA  | ၁၁၅  | מתכ  | GAA  | AGA  |
|-----------------------|----------------------|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
| מינים ווסי ווסינסינים | UGAGACU GCU CCACGGGC | ACGGGCA GAC UCUUGUCC                            | GGCAGCG GAU UGACCGGA                             | UACACCU GUC GCGUGAAG                             | CGUUCCA GUC UUUCAACA                             | GGAAGCA GCC GGUGCAGG                             | GAAGACG GUC CUAUCGGC                             | CCUAUCG GCU GUCCAUGA                           | AUCGGCU GUC CAUGAAAG                             | GAAGUCU GCU CGCUAUUU                             | AACCUCA GAU CUACGAAA                             | UCUAUCC GCU GGGCAGCA                             | GGUGGCU GAC UCUCAGAC                             | ACUCUCA GAC CCCUGGAA                             | AUCUACA GCU GCCGGGCC                             | UACAGCU GCC GGGCCUUC                             | UGUCACA GAU GUGCCGAA                             | GAUGCCA GCC GAAGGAGA                             |
|                       |                      | AGAA GCCCGU ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA | AGAA GCUGCC ACCAGAGAAACACAGGUUGUGGUACAUUACCUGGUA | AGAA GGUGUA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GGAACG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GCUUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GUCUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GAUAGG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA | AGAA GCCGAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GACUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GAGGUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GAUAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GCCACC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GAGAGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GUAGAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GCUGUA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GUGACA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGAA GGCAUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA |
|                       |                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|                       | 99097779             | GGACAAGA  | UCCGGUCA   | CUUCACGC   | UGUUGAAA   | CCUGCACC   | GCCGAUAG   | UCAUGGAC                                       | CUUUCAUG   | AAAUAGCG   | UUUCGUAG   | ກອດກອດ   | GUCUGAGA   | UUCCAGGG   | ວອອວວວອອ   | GAAGGCCC   | UUCGGCAC   | ncnccnnc   |
| 754                   | <b>,</b>             | 992   | 871  | 096  | 988  | 1051   | 1081   | 1090   | 1093   | 1169   | 1315   | 1363   | 1604   | 1612   | 1629   | 1632   | 1688   | 1730   |

2814

15

186 UCAAAACC UGAAACU GUC CUGUGUGG CGCCUCA GAU CACUUGGU GCACGCU GUU UAUUGAAA UACCUCAC UGAAGCG GUC UUCUUCCG UGGAGCU GAU CACGCUCA GGACCCA GAU GAAGUUCC GCU GCCCUAUG AACGGCU GCC CUAUGAUG CCCACCU GCC GGACUGUG AAAGACA GAC VACCUGUC GAC UGUGGCUG AAGCUCU GAU GACCGAAC GCCCUCU GAU GGUGAUCG CAACUACC UVAUUCU GUC UCAACAAG GGACGCA GCC UUGCAUAU AAGCCCC GCC UAGACAGU ပ္သည္ဟ GCU GNC CACACCU AAGCGCA GUGAACG CCUGCCG GAAACCU CCACACAG AGAA GUUUCA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGUGUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA ACCAAGUG AGAA GAGGCG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GCGUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GUGAGGUA AGAA GCGCUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UGAGCGUG AGAA GCUCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCUUCA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GACAGGUA AGAA GUCUUU ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGAACUUC AGAA GGGUCC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA AGAA GUUCAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CAUCAUAG AGAA GCCGUU ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA CACAGUCC AGAA GGUGGG ACCAGAGAAACACGGUGGUGGUACAUUACCUGGUA GGCAGG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GUUCGGUC AGAA GAGCUU ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CGAUCACC AGAA GAGGCC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA GGUAGUUG AGAA GGUUUC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA CUUGUUGA AGAA GAAUAA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA AUAUGCAA AGAA GCGUCC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA ACUGUCUA AGAA GGGCUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGUUUUGA AGAA UUUCAAUA AGAA CGGAAGAA AGAA CAGCCACA AGAA CAUAGGGC

1753

2176 2258 2305

ഗ

2383 2405 2432 2464 2467 2592 2596 2596 2596 2779

10

|     | GCACUCU GCU GGGCUCCC | GGGAGCCC AGAA GAGUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAGUGC | AGAA | GGGAGCCC      | 3772 |
|-----|----------------------|---|--------|------|---------------|------|
|     | ACUAUCA GCU GGACACUA | UAGUGUCC AGAA GAUAGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAUAGU | AGAA | UAGUGUCC      | 3754 |
|     | AAGCUCU GAU GAUGUGAG | CUCACAUC AGAA GAGCUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAGCUU | AGAA | CUCACAUC      | 3650 |
|     | CUUUGCA GAU CCACAUUU | GCAAAG ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA                 | GCAAAG | AGAA | AAAUGUGG AGAA | 3623 |
|     | AAGGACG GCU UUGCAGAU | AUCUGCAA AGAA GUCCUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GUCCUU | AGAA | AUCUGCAA      | 3615 |
|     | CCAUACU GAC UAGAAACA | UGUTUCUA AGAA GUAUGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GUAUGG | AGAA | UGUUUCUA      | 3553 |
|     | GUGACCU GCU UCAAGCCA | UGGCUUGA AGAA GGUCAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGUCAC | AGAA | UGGCUUGA      | 3496 |
|     | GGCCCCG GUU UGCUGAAC | GUUCAGCA AGAA GGGGCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | ລວອອອອ | AGAA | GUUCAGCA      | 3463 |
|     | GCAUGCG GAU GAGAACCC | GGGUUCUC AGAA GCAUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCAUGC | AGAA | ວດວດດວອອ      | 3379 |
|     | UGCAGCC GCC UGAAGGAA | UUCCUUCA AGAA GCUGCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCUGCA | AGAA | UUCCUUCA      | 3360 |
| 4.0 | UNCUGCA GCC GCCUGAAG | CUUCAGGC AGAA GCAGAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCAGAA | AGAA | CUUCAGGC      | 3357 |
|     | GAACCCU GAU UAUGUGAG | CUCACAUA AGAA GGGUUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGGUUC | AGAA | CUCACAUA      | 3179 |
|     | AGUUUCU GUC CUCCAGAA | UUCUGGAG AGAA GAAACU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAAACU | AGAA | UUCUGGAG      | 3064 |
|     | UCCUACA GUU UCCAAGUG | GUAGGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA               | GUAGGA | AGAA | CACUUGGA AGAA | 3033 |
|     | AAGACCU GAU UUCCUACA | UGUAGGAA AGAA GGUCUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGCCCC | AGAA | UGUAGGAA      | 3022 |
|     | CCAAGCA GCC CCUCACCA | UGGUGAGG AGAA GCUUGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | gcnngg | AGAA | UGGUGAGG      | 3001 |
|     | AGCUCCA GCU UCCCUGAA | UUCAGGGA AGAA GGAGCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGAGCU | AGAA | UUCAGGGA      | 2934 |
|     | GUCACCA GCU CCAGCUUC | GAAGCUGG AGAA GGUGAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGUGAC | AGAA | GAAGCUGG      | 2928 |
|     | GUCAGCA GCU CAAGUGUC | GACACUUG AGAA GCUGAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCUGAC | AGAA | GACACUUG      | 2913 |

|   |   |   |   |   |   |                      |                      |                      | 188   | 3    |                      |                      |   |   |   |   |   |   |
|---|---|---|---|---|---|----------------------|----------------------|----------------------|---|------|----------------------|----------------------|---|---|---|---|---|---|
| UGAAGCG GUU CACCUGGA  | ACUUUCC GAU CUGCCGAG  | CCGAUCU GCC GAGGCCCA  | AGGCCCA GCU UCUGCUILC                                       | AGCUUCU GCU UCUCCAGC                                      | UUCUCCA GCU GUGGCCAC                                    | GAGUCCU GCU GUUCUCCA | UCCUGCU GUU CUCCACCC | ACCCCCA GAC UACAACUC |   |      | CUCACCA GCC CCGACAAC | ACAACCA GCC CCUGACAG | CUAUUCC GCU CCACAGGA                                      | GGAGCCA GCU GCUUUCG                                       | GCCAGCU GCU UUUCGUGA                                      | UGUUGCU GIIII IIIICACIIAA                                 | GGGGACC GCC CGCCCAC                                       | ACCGCCC GCC CACCGGCC                                      |
| 6 UCCAGGUG AGAA GCUUCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | 1 CUCGGCAG AGAA GAAAGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | s UGGGCCUC AGAA GAUCGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | 7 GAAGCAGA AGAA GGGCCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCUGGAGA AGAA GAAGCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GUGGCCAC AGAA GGAGAA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA |                      |                      |                      | UNUAGGCG AGAA GGGAGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA |      |                      |                      | UCCUGUGG AGAA GAAUAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CGAAAAGC AGAA GGCUCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UCACGAAA AGAA GCUGGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UVAGUCAA AGAA GCAACA ACCAGAGAAACACACGUUGUGGUACAUVACCUGGUA | GGUGGGCG AGAA GUCGCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGCCGGUG AGAA GGCGGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA |
| 3796  | 3881  | 3886  | 3897  | 3903  | 3912  | 3969                 | 3972                 | 3986                 | 4018  | 4022 | 4040                 | 4053                 | 4095  | 4110  | 4113  | 4168  | 4290  | 4294  |

AGUCCCAC AGAA GCAGGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCCUGCA GCU GUGGGACU

4329

ហ

| 4378 | CAGAGCAG | AGAA | GUGCAU | AGAA GUGCAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA          | AUGCACU GAC CUGCUCUG   |
|------|----------|------|--------|---|------------------------|
| 4383 | AGAGACAG | AGAA | GGUCAG | AGAA GGUCAG ACCAGAGAAACACGCUUGUGGUACAUUACCUGGUA           | CUGACCU GCU CUGUCUCU   |
| 4388 | AUAAGAGA | AGAA | GAGCAG | AUAAGAGA AGAA GAGCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CUGCUCU GUC UCUCUNAU   |
| 4457 | CUCCACAG | AGAA | GACGCA | CUCCACAG AGAA GACGCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UGCGUCC GUC CUGUGGAG   |
| 4525 | CCCGAAAC | AGAA | GAGGCC | CCCGAAAC AGAA GAGGCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | eeccncc ecn ennnceee   |
| 4528 | GGGCCCGA | AGAA | GCGGAG | GGGCCCGA AGAA GCGGAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | cocceco eno oceeecc    |
| 4643 | AAACAGAC | AGAA | GAAGAC | AAACAGAC AGAA GAAGAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | gucunca gua gucagana   |
| 4650 | GGAUGGUA | AGAA | GACAAC | GGAUGGUA AGAA GACAAC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GUUGUCU GUU UACCAUCC   |
| 4724 | ACUAGAGG | AGAA | GAUGAU | ACUAGAGG AGAA GAUGAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AUCAUCA GUU CCUCUAGU 8 |
| 4771 | AUGCGAAG | AGAA | GGCCNG | AUGCGAAG AGAA GGCCUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CAGGCCU GAC CUUCGCAU   |
| 4785 | nccccene | AGAA | GUAUGC | UCCCCGUG AGAA GUAUGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCAUACU GCU CACGGGGA   |
| 4809 | CUAGGCCA | AGAA | GGACCA | CUAGGCCA AGAA GGACCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UGGUCCA GUU UGGCCUAG   |
| 4834 | UUGAGCCC | AGAA | GUAGGC | AGAA GUAGGC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA            | GCCUACU GAU GGGCUCAA   |
| 4912 | AUAUAUAA | AGAA | GGAUAA | AUAUAUAA AGAA GGAUAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UNAUCCU GUU UUAUAU     |
| 5119 | UCCUCUCA | AGAA | accona | UCCUCUCA AGAA GCCUUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | CAAGGCA GUC UGAGAGGA   |
| 5144 | UAAAUAUG | AGAA | GAUACU | UAAAUAUG AGAA GAUACU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | AGUAUCA GCC CAUAUUUA   |
| 5287 | AGGUAUGA | AGAA | GAUGAA | AGGUAUGA AGAA GAUGAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | UUCAUCU GUU UCAUACCU   |
| 5363 | CCCCAAAG | AGAA | GGCACC | CCCCAAAG AGAA GGCACC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | Geneces een conneege   |

10

| UGGUUCU GCU UAAAGACU | AGUCUUUA AGAA GAACCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAACCA  | AGAA | AGUCOOOA | 0100 | 0   |
|----------------------|---|---------|------|----------|------|-----|
| UVAUUCC GAU UUUAAUAA | UNAUUAAA AGAA GAAUAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAAUAA  | AGAA | UUAUUAAA | 5915 | 4.1 |
| AACAGCA GCC UGAGGUUU | AAACCUCA AGAA GCUGUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCUGUU  | AGAA | AAACCUCA | 5842 |     |
| AGAAACG GAU GAGAACAG | LUGUUCUC AGAA GUUUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | Guanca  | AGAA |          | 0029 |     |
| CUVGUCG GCU GCAGUGUG | CACACUGE AGAA GACAAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GACAAG  | AGAA | CACACUGC | 18/6 |     |
| GCCUGCA GCC CACUGUGG | CCACAGUG AGAA GCAGGC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCAGG   | AGAA | CCACAGUG | 5646 | >   |
| UGAGACA GCC UGCAGCCC | GGGCUGCA AGAA GUCUCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | 30C0C   | AGAA | GGGCUGCA | 5639 |     |
| UCUGUCU GAU GAGACUGG | CCAGUCUC AGAA GACAGA ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA   | GACAG   | AGAA | CCAGUCUC | 5601 |     |
| GUUUUCU GUC UGAUGAGA | UCUCAUCA AGAA GAAAAC ACCAGAGAAACACGUUGUGGUACAUUACCUGGUA   | GAAAA   | AGAA | UCUCAUCA | 5597 |     |
| GGUACCU GCU CCCCUGUG | CACAGGGG AGAA GGUACC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GGUAC   | AGAA | CACAGGGG | 5564 |     |
| AUUCUCU GAC CGGGCCAG | CUGGCCCG AGAA GAGAAU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GAGAAI  | AGAA | CUGGCCCG |      | S   |
| AAUAGCU GCU UUGGGAGA | UCUCCCAA AGAA GCUAUU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA | GCUAU   | AGAA | UCUCCCAA | 5500 |     |
| CUGGGCA GAC GAUGAAUA | UAUUCAUC AGAA GCCCAG ACCAGAGAAACACGCUUGUGGUACAUUACCUGGUA  | GCCCA(  | AGA  | UAUUCAUC | 5486 |     |
| GGUCACA GCU GGGCAGAC | GUCUGCCC AGAA GUGACC ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA  | GUGAC   | AGA  | GNCNGCCC | 5478 |     |
| CACACCU GCC GGAGCCGG | CCGGCUCC AGAA GGUGUG ACCAGAGAACACACGUUGUGGUACAUUACCUGGUA  | v GGUGU | AGA. | CCGGCACC | 5462 |     |

Table X: Homologous Hammerhead Ribozyme Target Sites

Between Human flt-1 and KDR RNA

|    | nt.   | flt-1             | nt.   | KDR               |
|----|-------|-------------------|-------|-------------------|
|    | Posi- | Target Sequence   | Posi- | Target Sequence   |
| 5  | tion  |                   | tion  |                   |
|    | 3388  | CCGGGAU A UUUAUAA | 3151  | CCGGGAU A UUUAUAA |
|    | 2174  | AAUGUAU A CACAGGG | 3069  | Aguguau c Cacaggg |
|    | 2990  | UGCAAAU A UGGAAAU | 2756  | UGCAAAU u UGGAAAc |
|    | 2693  | CUCCCUU A UGAUGCC | 2459  | CUGCCUU A UGAUGCC |
| 10 | 2981  | GUUGAAU A CUGCAAA | 2747  | GUgGAAU u CUGCAAA |
|    | 1359  | UAUGGUU A AAAGAUG | 2097  | UgUGGUU u AAAGAUa |
|    | 3390  | GGGAUAU U UAUAAGA | 3153  | GGGAUAU U UAUAAag |
|    | 3391  | GGAUAUU U AUAAGAA | 3154  | GGAUAUU U AUAAagA |
|    | 2925  | ACGUGGU U AACCUGC | 2691  | Auguggu c AACCuuC |
| 15 | 7140  | UAUUUCU A GUCAUGA | 2340  | UACUUCU u GUCAUCA |
|    | 1785  | CAAUAAU A GAAGGAA | 1515  | CucUAAU u GAAGGAA |
|    | 2731  | GAGACUU A AACUGGG | 768   | uuGACUU c AACUGGG |
|    | 3974  | GAUGACU A CCAGGGC | 1466  | GAgGACU u CCAGGGa |
|    | 6590  | UUAAUGU A GAAAGAA | 2603  | aaAAUGU u GAAAGAA |
| 20 | 6705  | GCCAUUU A UGACAAA | 3227  | aCaAUUU u UGACAgA |
|    | 974   | GUCAAAU U ACUUAGA | 147   | uUCAAAU U ACUUgcA |
|    | 1872  | AUAAAGU U GGGACUG | 1602  | AcAAAGU c GGGAgaG |
|    | 2333  | ACUUGGU U UAAAAAC | 1088  | AaaUGGU a UAAAAAu |
|    | 2775  | AAGUGGU U CAAGCAU | 1745  | AcaUGGU a CAAGCuU |
| 25 | 3533  | UUCUCCU U AGGUGGG | 3296  | UUuUCCU U AGGUGcu |
|    | 3534  | UCUCCUU A GGUGGGU | 3297  | UuUCCUU A GGUGcuU |
|    | 3625  | GUACUCU A CUCCUGA | 4054  | GagCUCU c CUCCUGu |
|    | 1814  | AGCACCU U GGUUGUG | 1059  | AGUACCU U GGUUacc |
|    | 2744  | GGCAAAU C ACUUGGA | 147   | uuCAAAU u ACUUGcA |
| 30 | 2783  | CAAGCAU C AGCAUUU | 796   | gAAGCAU C AGCAUaa |

192

|    | 3613 | GAGAGCU C CUGAGUA | 2968 | GgaAGCU C CUGAagA |
|----|------|-------------------|------|-------------------|
|    | 4052 | AAGGCCU C GCUCAAG | 1923 | ucuGCCU u GCUCAAG |
|    | 5305 | UCUCCAU A UCAAAAC | 456  | ggUCCAU u UCAAAuC |
|    | 7158 | AUGUAUU U UGUAUAC | 631  | gucuauu a uguacau |
| 5  | 1836 | CUAGAAU U UCUGGAA | 1007 | aUgGAAU c UCUGGug |
|    | 2565 | CUCUCUU C UGGCUCC | 2328 | uguUCUU C UGGCUaC |
|    | 4250 | CUGUACU C CACCCCA | 3388 | uUaUACU a CACCagA |
|    | 7124 | ACAUGGU U UGGUCCU | 3778 | cagUGGU a UGGUuCU |
|    | 436  | AUGGUCU U UGCCUGA | 1337 | AcGGUCU a UGCCauu |
| 10 | 2234 | GCACCAU A CCUCCUG | 1344 | augCCAU u CCUCCcc |
|    | 2763 | GGGCUUU U GGAAAAG | 990  | uuGCUUU U GGAAguG |
|    | 4229 | CCAGACU A CAACUCG | 767  | auuGACU u CAACUgG |
|    | 5301 | GUUUUCU C CAUAUCA | 3307 | ugcuucu c cauauce |
|    | 6015 | AGAAUGU A UGCCUCU | 1917 | AcuAUGU c UGCCUug |
| 15 | 6095 | AUUCCCU A GUGAGCC | 1438 | AUaCCCU u GUGAaga |
|    | 6236 | UGUUGUU C CUCUUCU | 76   | UagUGUU u CUCUUga |
|    | 5962 | GCUUCCU U UUAUCCA | 3099 | auaUCCU c UUAUCgg |
|    | 7629 | UAUAUAU U CUCUGCU | 3096 | gAaAUAU c CUCUuaU |
|    |      |                   |      | 5 0000000         |

Lowercase letters are used to represent sequence variance 20 between flt-1 and KDR RNA

193

|   | Table XI: 2.5 μmol | RNA Synthesis | Cycle          |            |
|---|--------------------|---------------|----------------|------------|
|   | Reagent            | Equivalents   | Amount         | Wait Time* |
|   | Phosphoramidites   | 6.5           | 163 <i>µ</i> L | 2.5        |
|   | S-Ethyl Tetrazole  | 23.8          | 238µL          | 2.5        |
| 5 | Acetic Anhydride   | 100           | 233 μL         | 5 sec      |
|   | N-Methyl Imidazole | 186           | 233 μL         | 5 sec      |
|   | TCA                | 83.2          | 1.73 mL        | 21 sec     |
|   | Iodine .           | 8.0           | 1.18 mL        | 45 sec     |
|   | Acetonitrile       | NA            | 6.67 mL        | NA         |

194

## Claims

 Nucleic acid molecule which modulates the synthesis, expression and/or stability of an mRNA encoding one or more receptors of vascular endothelial growth
 factor.

- The nucleic acid of claim 1, wherein said receptor is flt-1, KDR and/or flk-1.
- 3. The nucleic acid of claim 1 or 2, wherein said molecule is an enzymatic nucleic acid molecule.
- 4. The nucleic acid molecule of claim 3, wherein, the binding arms of said enzymatic nucleic acid contain sequences complementary to the substrate nucleotide base sequences in any one of Tables II to IX.
- The nucleic acid molecule of claims 3 or 4,
   wherein said nucleic acid molecule is in a hammerhead motif.
- The enzymatic nucleic acid molecule of claim 3 or 4, wherein said nucleic acid molecule is in a hairpin, hepatitis Delta virus, group I intron, VS nucleic acid or RNaseP nucleic acid motif.
  - 7. The enzymatic nucleic acid molecule of any of claims 3 or 4, wherein said ribozyme comprises between 12 and 100 bases complementary to the RNA of said region.
- 8. The enzymatic nucleic acid of claim 7, wherein 25 said ribozyme comprises between 14 and 24 bases complementary to the RNA of said region.
  - 9. Enzymatic nucleic acid molecule consisting essentially of any ribozyme sequence selected from those shown in Tables II to IX.

- 10. A mammalian cell including a nucleic acid molecule of any of claims 1, 2 or 3.
- 11. The cell of claim 10, wherein said cell is a human cell.
- 12. An expression vector comprising nucleic acid encoding the nucleic acid molecule of any of claims 1, 2, 3 or 4, in a manner which allows expression and/or delivery of that RNA molecule within a mammalian cell.
- 13. The expression vector of claim 12, wherein said 10 nucleic acid is an enzymatic nucleic acid.
  - 14. A mammalian cell including an expression vector of any of claims 12 or 13.
  - 15. The cell of claim 14, wherein said cell is a human cell.
- 15 16. A method for treatment of a patient having a condition associated with the level of flt-1, KDR and/or flk-1, wherein the patient, tissue donor or population of corresponding cells is administered a therapeutically effective amount of an enzymatic nucleic acid molecule of claims 1, 2, 3 or 4.
  - 17. A method for treatment of a condition related to the level of flt-1, KDR and/or flk-1 activity by administering to a patient an expression vector of claim 12.
- 18. The method of claims 16 or 17, wherein said 25 patient is a human.
  - 19. The nucleic acid of claim 1 or 2, wherein said molecule is an antisense nucleic acid molecule.

- 20. The nucleic acid molecule of claim 19, wherein, said antisense nucleic acid contain sequences complementary to the substrate nucleotide base sequences in any one of Tables II to IX.
- 21. An expression vector comprising nucleic acid encoding the antisense nucleic acid molecule of any one of claims 19 or 20, in a manner which allows expression and/or delivery of that antisense RNA molecule within a mammalian cell.
- 22. A mammalian cell including an expression vector of claim 21.
  - 23. The cell of claim 22, wherein said cell is a human cell.

SUBSTITUTE SHEET (RULE 26)

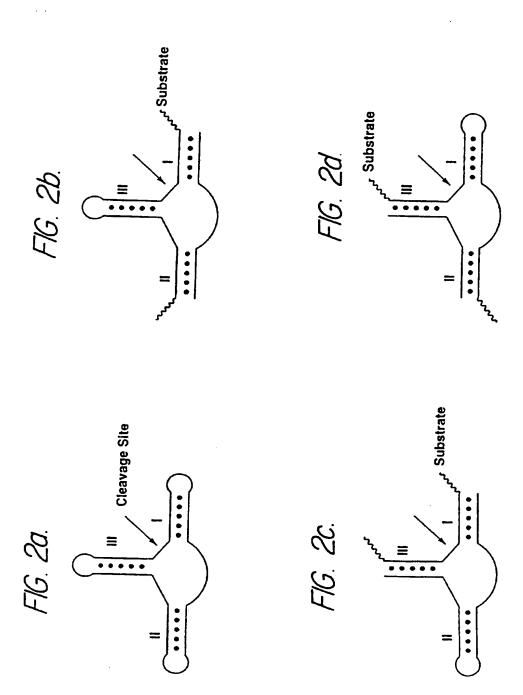
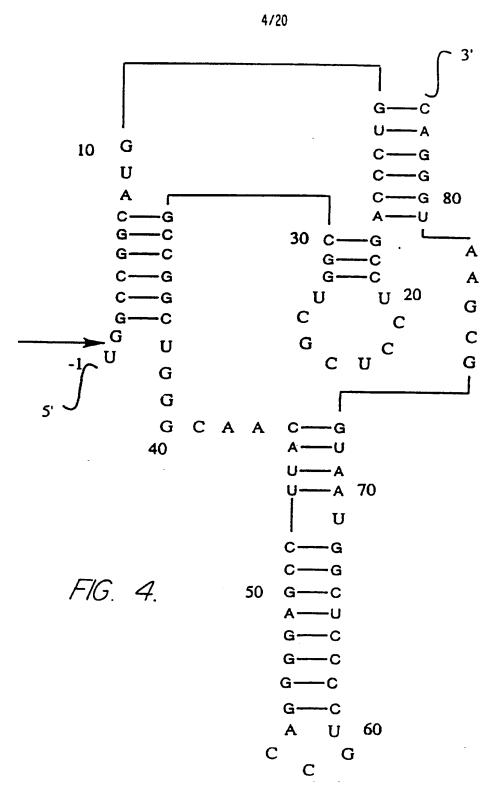


FIG. 3.



SUBSTITUTE SHEET (RULE 26)

## **NEUROSPORA VS RNA ENZYME**

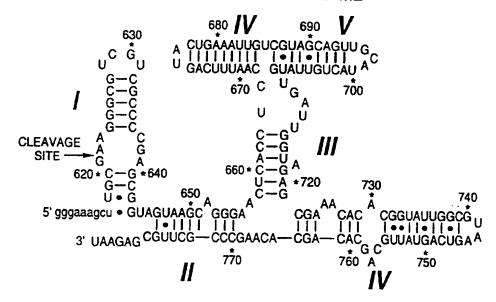
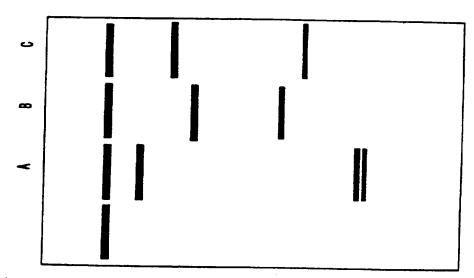
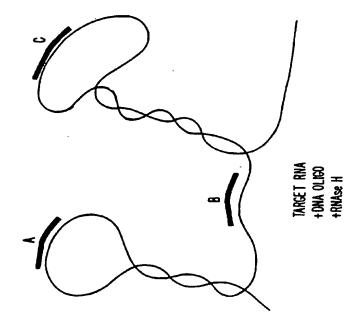


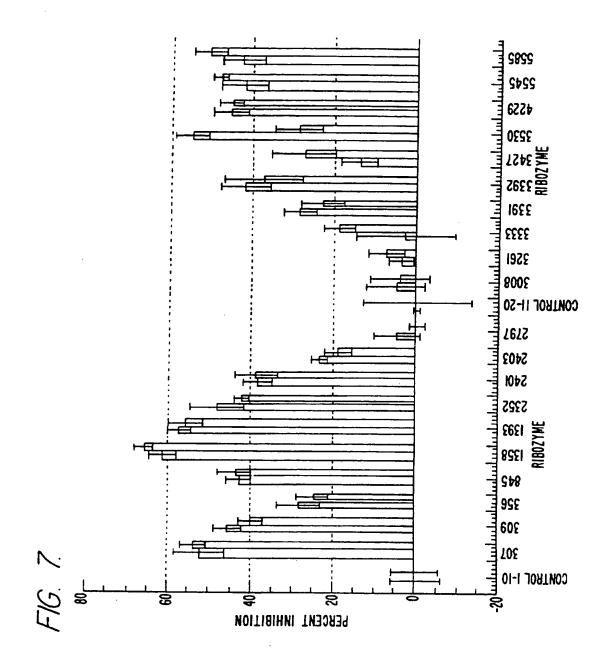
FIG. 5.



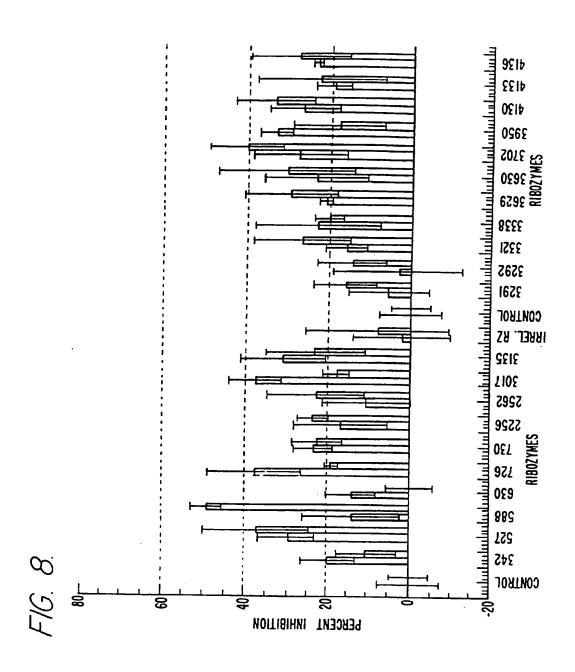
FIG



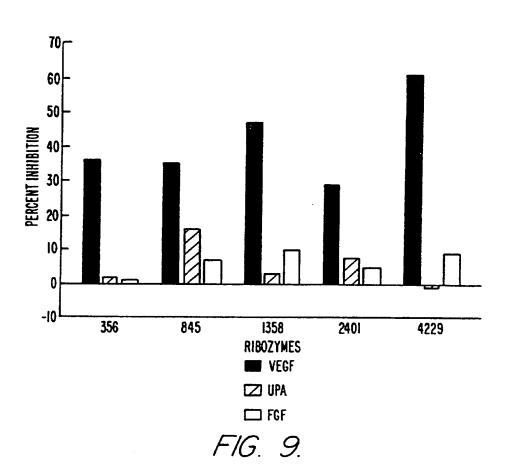
SUBSTITUTE SHEET (RULE 26)

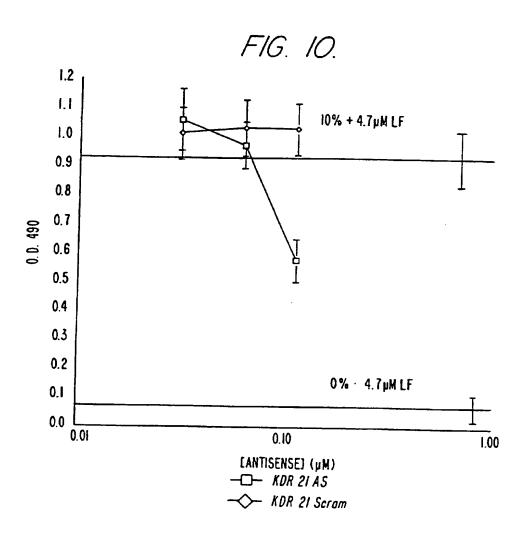


SUBSTITUTE SHEET (RULE 26)

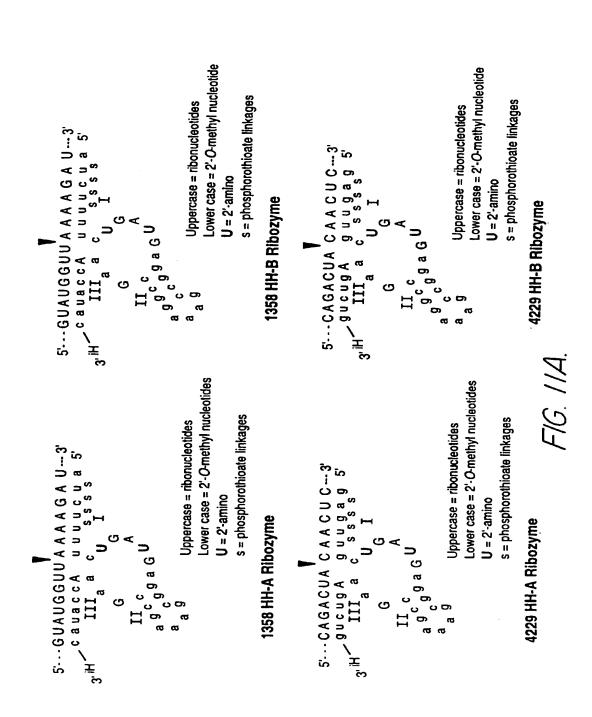


SUBSTITUTE SHEET (RULE 26)

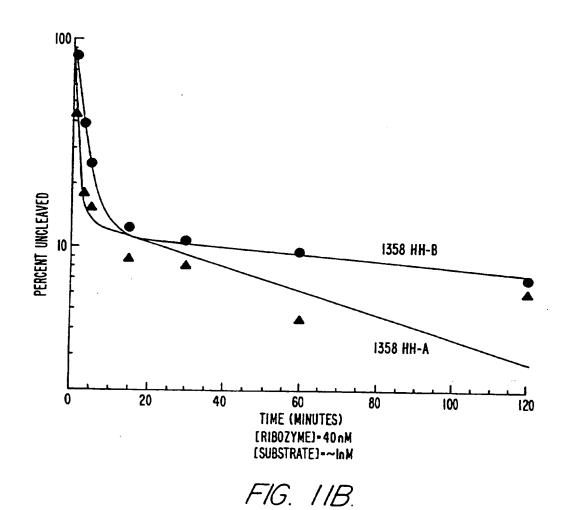




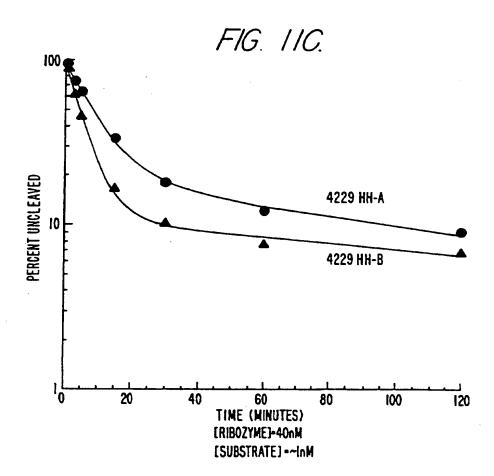
SUBSTITUTE SHEET (RULE 26)

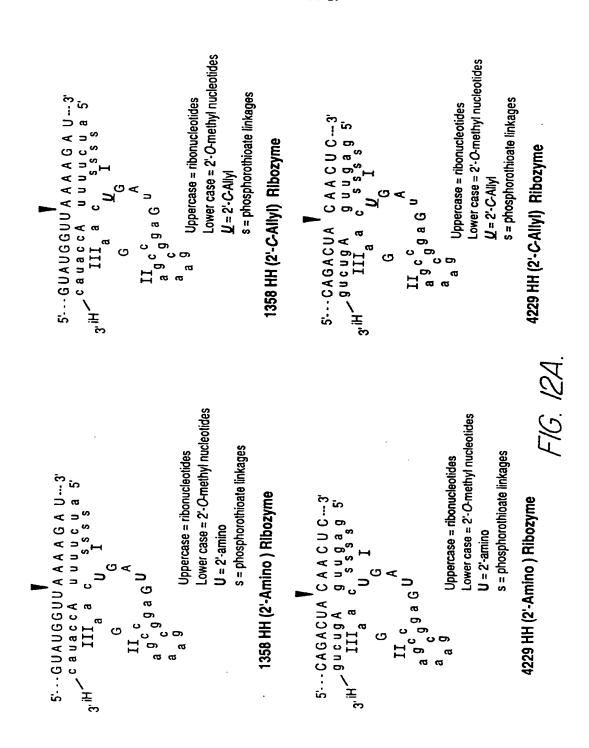


SUBSTITUTE SHEET (RULE 26)

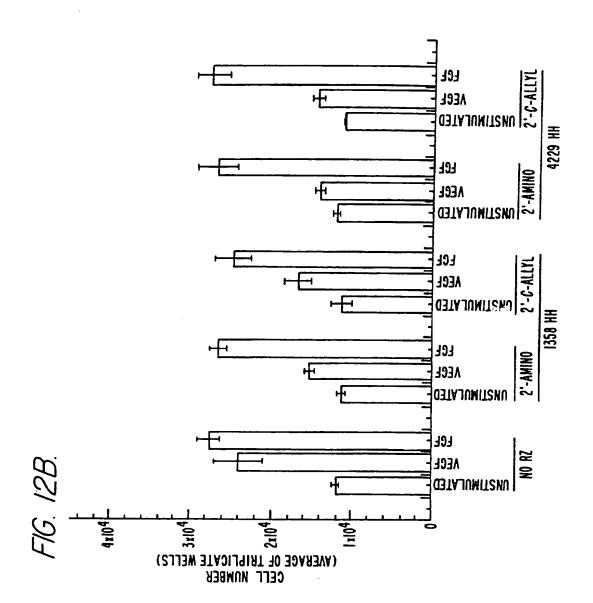


**SUBSTITUTE SHEET (RULE 26)** 

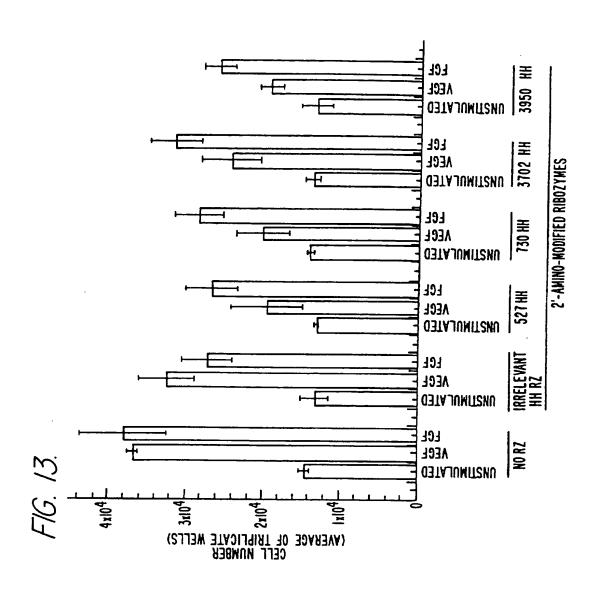




SUBSTITUTE SHEET (RULE 26)

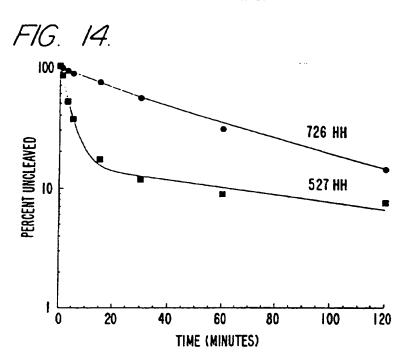


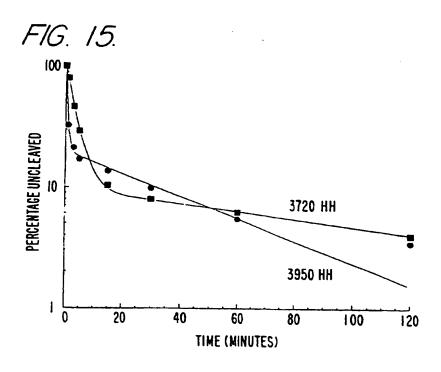
SUBSTITUTE SHEET (RULE 26)



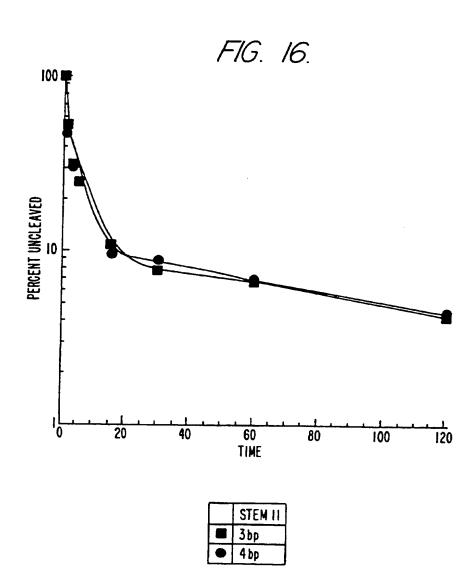
SUBSTITUTE SHEET (RULE 26)



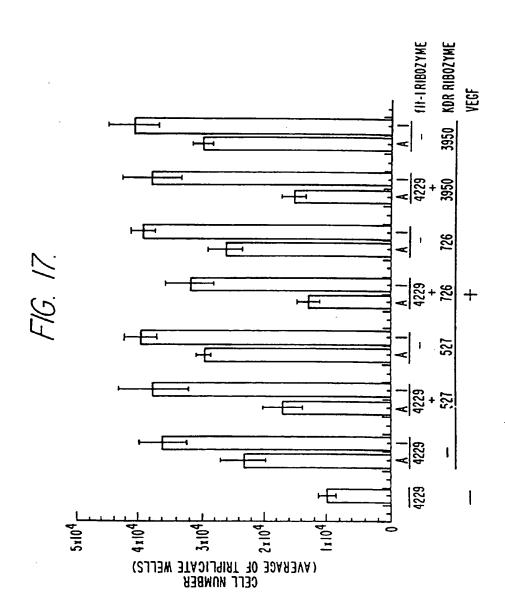




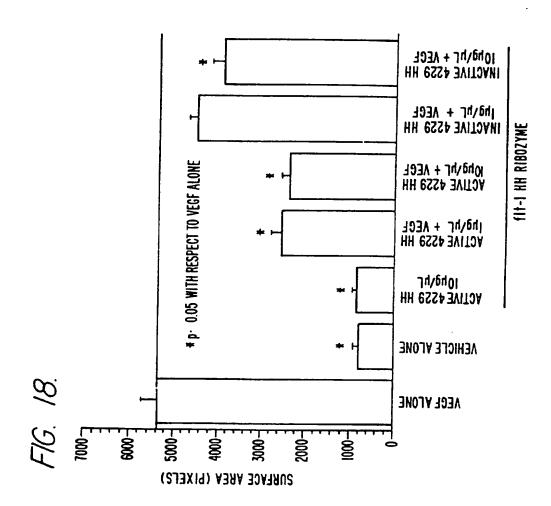
SUBSTITUTE SHEET (RULE 26)



SUBSTITUTE SHEET (RULE 26)



SUBSTITUTE SHEET (RULE 26)



**SUBSTITUTE SHEET (RULE 26)**